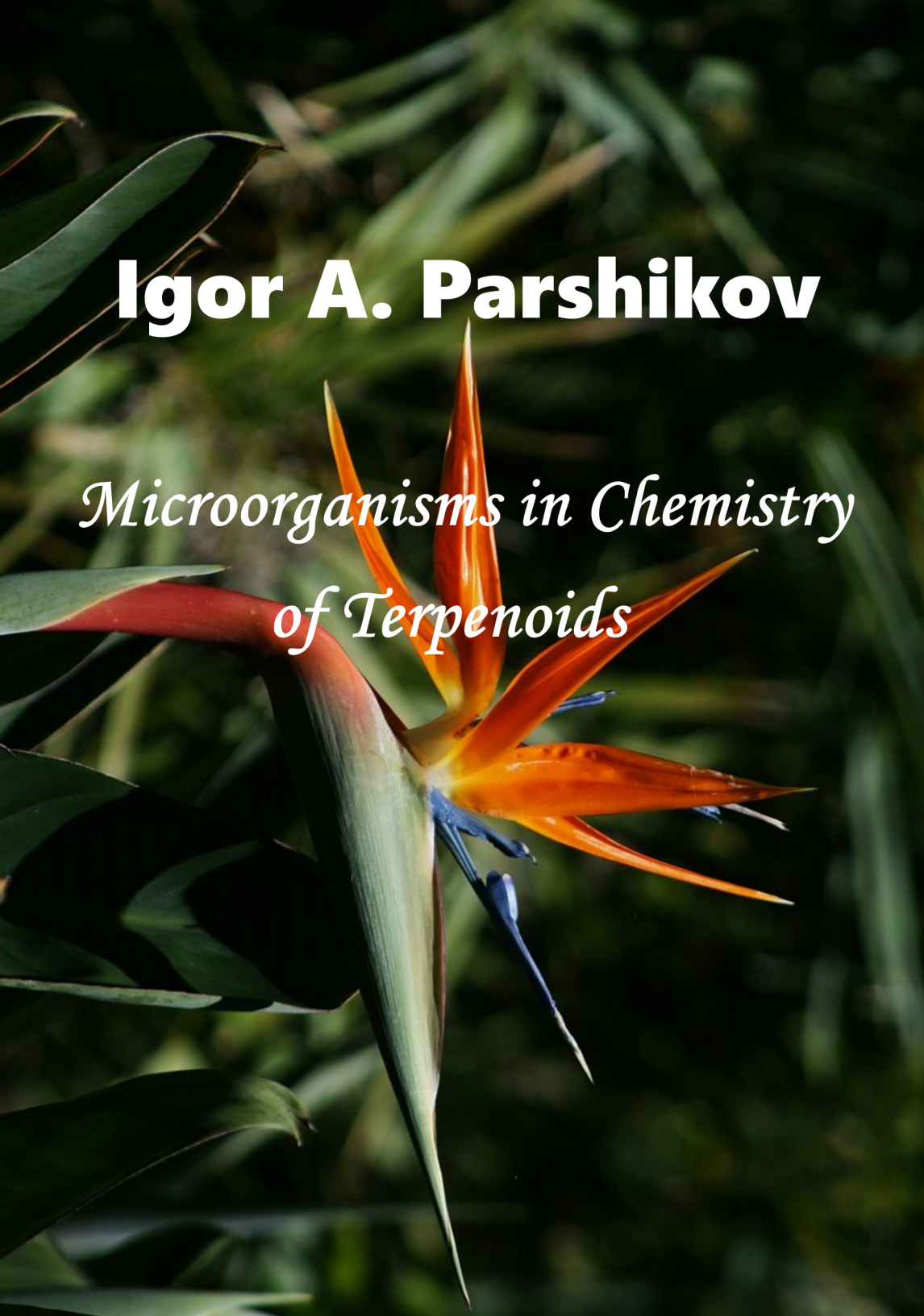

Igor A. Parshikov

Microorganisms in Chemistry of Terpenoids

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Microorganisms in Chemistry of Terpenoids

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The monograph describes examples of the application of microbial technology for obtaining of derivatives of terpenoids. Obtaining new derivatives of terpenoids, including artemisinin derivatives with increased antimalarial activity, is an important goal of research in microbial biotechnology and medicinal chemistry.

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Introduction

The transformation of organic compounds by microbial cultures has long been of interest to the pharmaceutical, chemical and food industries because of numerous advantages compared to chemical synthesis (Pandey et al., 2000; Parshikov et al., 1994; 2010; Parshikov, 2015; Silva et al., 2014).

Terpenoids are components of the essential oils of plants; they are derivatives of terpene hydrocarbons, which are combinations of five-carbon isoprene units (Newman, 1972; Dewick, 2001). They have been classified into monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids. Several of these groups of terpenoids are found in the essential oils of plants that are used in traditional medicine to treat malaria and other fevers (Titanji et al., 2008; Kaur et al., 2009; Khamsan et al., 2011). The large variety of terpenoids, mostly derived from plants, that have been purified and shown to have antiplasmodial activity in vitro has been discussed extensively in recent review articles (Batista et al., 2009; Bero et al., 2009; Kaur et al., 2009; Chaturvedi, 2011; Harinasuta et al., 1965; Kain, 1995; Klassen, 2009; Nogueira and Lopes, 2011; Snow et al., 2005). Information about the comparative activities of most of these natural terpenoids and their derivatives in different *Plasmodium* spp., however, is difficult to obtain because of data security practices for potential commercial drugs.

Among the sesquiterpenoids, artemisinin and its derivatives are useful and effective drugs against most chloroquine-resistant strains of *P. falciparum* (Klayman, 1985). However, problems associated with artemisinin, including low solubility in water and even in oil (Luo and Shen, 1987; Hien and White, 1993; Vroman et al., 1999), have prompted scientists to seek new artemisinin derivatives. Some of these artemisinin-derived drugs have been reported to be neurotoxic to animals when injected (Vroman et al., 1999; Gordi and Lepist, 2004; Liao, 2009; Medhi et al., 2009; Mannan et al., 2010). There is also evidence of reproductive toxicity of artemisinin derivatives at high doses in animals (Medhi et al., 2009; Clark, 2011). Increasing resistance of malaria parasites to currently used drugs, including *P. vivax* resistance to chloroquine and primaquine in parts of New Guinea, Asia, and Africa (Price et al., 2011) and *P. falciparum* resistance to artemisinin in western Cambodia, eastern Thailand, and some nearby areas (Noedl et al., 2008; Wongsrichanalai and Meshnick, 2008; Dondorp et al., 2010; O'Brien et al., 2011), is another important reason for developing new antimalarial drugs.

Some artemisinin analogs may be obtained by semisynthetic processes; for example, artemisinin can be easily reduced chemically to the more effective, but neurotoxic, dihydroartemisinin (Klayman, 1985; Vroman et al., 1999; Avery et al., 2002). Other structural changes in artemisinin remain a

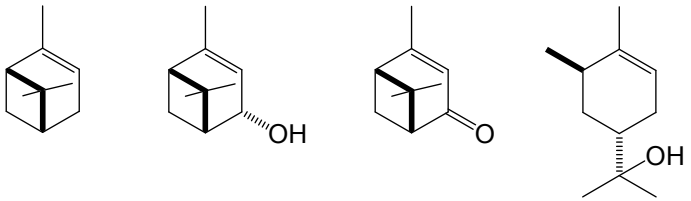
challenge for chemists because of the difficulty of introducing specific functional groups by conventional synthetic methods.

Many microorganisms, especially certain fungi, have the ability to transform terpenoids regioselectively and stereoselectively (Sutherland, 2004; Carvalho and Fonseca, 2006; Simeó and Sinisterra, 2009; Parshikov, 2012). In this book to outline some of the great variety of modifications, that can be expected from the use of microorganisms for the transformation of terpenoids. The biochemical mechanisms have scarcely been investigated, but it seems likely that cytochromes P450 and perhaps dioxygenases will be found to be involved in many of the transformations (Martin et al., 2008; Krings et al., 2009). It is our hope that further developments in microbial biotechnology, including the discovery of new strains with unique enzyme systems for the transformation of terpenoids, may make it possible to derive a variety of newer and more useful drugs from those now available.

1. Transformation of monoterpenoids

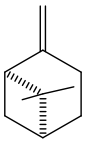
In the leaves of lemon grass, *Cymbopogon citratus*, there is an essential oil that inhibits the growth of *Plasmodium berghei*, a species which does not infect humans, with 86.6% of the activity of chloroquine (Tchoumbougnang et al., 2005). This oil contains several monoterpenoids, with citral (geranial and neral), β-myrcene, geraniol, nerol, citronellal and limonene as the main components (Schaneberg and Khan, 2002). Limonene has been shown to have antimalarial activity because it inhibits the isoprenylation of proteins in *P. falciparum* (Moura et al., 2001).

(+)-α-Pinene (**I**) is a monoterpene, produced by pine trees and many other plants, that acts as an insect repellent. The **(+)-** isomer is oxidized by a strain of *A. niger* to the floral fragrances (+)-*cis*-verbenol (**II**, yield 20-25%) and (+)-verbenone (**III**, yield 2-3%) and the mucolytic agent (+)-*trans*-sobrerol (**IV**, yield 2-3%), in 4-8 h (Bhattacharyya et al., 1960):



I **II** **III** **IV**

Another strain of *A. niger* produces nonadecanol from (+)-α-pinene and also metabolizes the enantiomer (−)-α-pinene (Divyashree et al., 2006). A different natural isomer, (−)-β-pinene (**V**), is oxidized by *A. niger* ATCC 9642 in liquid cultures to produce the fragrance and flavoring agent α-terpineol (**VI**, yield about 4%) in 3 days (Toniazzo et al., 2005):



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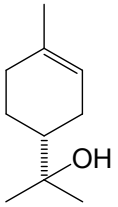
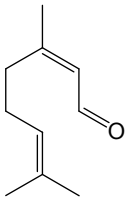
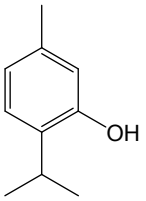


VI

Fungi of the genera *Aspergillus* and *Penicillium* may transform citral and other monoterpenoids to various products (Demyttenaere and De Pooter, 1998; Demyttenaere et al., 2000; Esmaeili and Tavassoli, 2010). For example, a *Penicillium* sp. transformed citral (**VII**) in 21 days to a mixture of six different monoterpenoids with a total yield of 67.4%, including thymol (**VIII**, 21.5%), limonene (**IX**, 3.1%), α-pinene (**I**, 3.7%), geraniol (**X**, 6.8%), geranial (**XI**, 18.6%) and nerol (**XII**, 13.7%) (Esmaeili and Tavassoli, 2010):



VII



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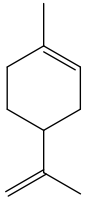

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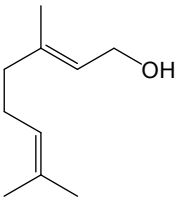
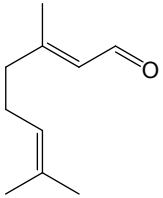


X



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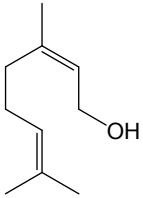
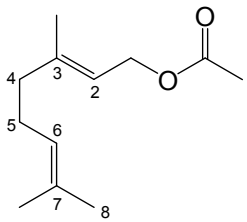


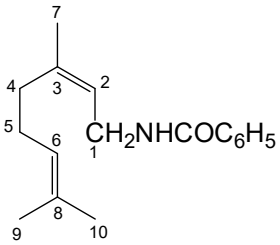
XII

Geranyl acetate **(XIII)** is metabolized by *A. niger* to geraniol (**X**) and 8-hydroxygeraniol, with 50% and 40% yield, respectively (Madyastha et al., 1988):

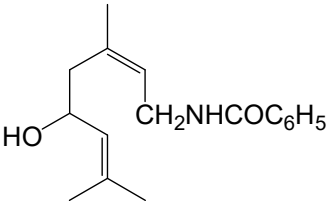


XIII

The transformation of citral benzamide (**XIV**) during 72 hours by fungi *Cunninghamella verticillata* VKPM F-430 and *Beauveria bassiana* VKM F-3111D showed formation of 5-hydroxycitral benzamide (**XV**) in 20% yield (Parshikov et al., 1990a,b):

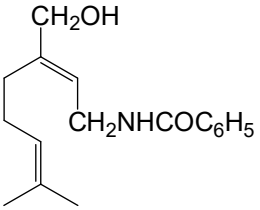


XIV

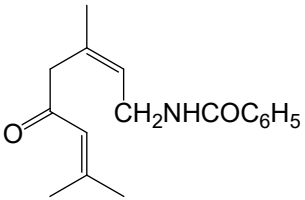


XV

In same time the transformation of citral benzamide (**XIV**) by fungus *Scopulariopsis brevicaulis* VKM F-406 showed formation of 7-hydroxymethyl derivative (**XVI**) in 20% yield and 5-oxo- derivative (**XVII**) in 30% yield (Parshikov et al., 1993):

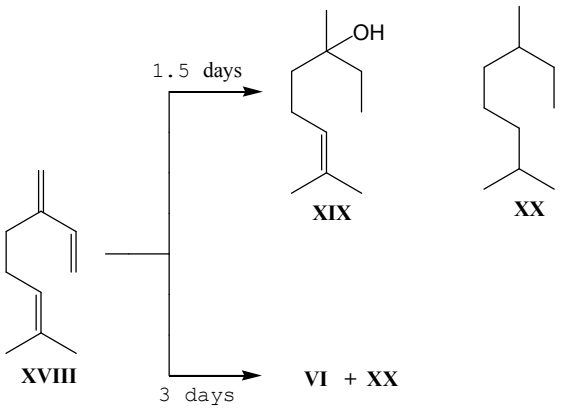


XVI

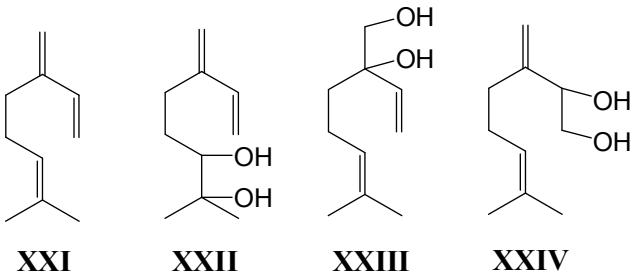


XVII

In the transformation of myrcene (**XVIII**) by the bacterium *Pseudomonas aeruginosa* PTCC 1074, formation of the products depended on the time of transformation. After 1.5 days the products found were dihydrolinalool (**XIX**, 79.5%) and 2,6-dimethyloctane (**XX**, 9.3%), whereas after 3 days they were α-terpineol (**VI**, 7.7%) and 2,6-dimethyloctane (**XX**, 90.0%) (Esmaeili and Hashemi, 2011):



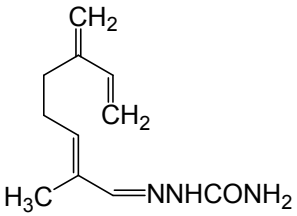
β-Myrcene (**XXI**), an acyclic monoterpene from plant essential oils, is transformed by *A. niger* JTS 191 at each of the three double bonds to produce three fragrant isomeric diols: 2-methyl-6-methylene-7-octene-2,3-diol (**XXII**), 6-methyl-2-ethenyl-5-heptene-1,2-diol (**XXIII**), and 7-methyl-3-methylene-6-octene-1,2-diol (**XXIV**) (Yamazaki al., 1988):



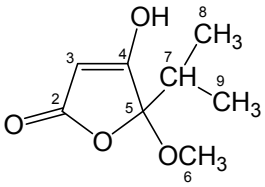
XXI **XXII** **XXIII** **XXIV**

It has been observed that a suspension of non-multiplying *Penicillium simplicissimum* selectively converted myrcenal semicarbazone (**XXV**) into 4-hydroxy-5-isopropyl-5-methoxy-2-

oxo-2,5-dihydrofuran (**XXVI**) with 84% yield (Parshikov et al., 1994, 2010):

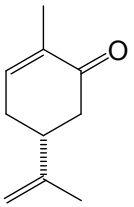


XXV

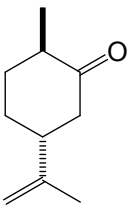


XXVI

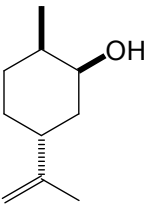
(−)-Carvone (**XXVII**) from spearmint oil is transformed stereoselectively to (+)-dihydrocarvone (**XXVIII**) and (+)-neodihydrocarveol (**XXIX**) by a strain of *A. niger* (Noma and Nonomura, 1974); similar products are produced from (+)-carvone (Noma and Nonomura, 1974):



XXVII



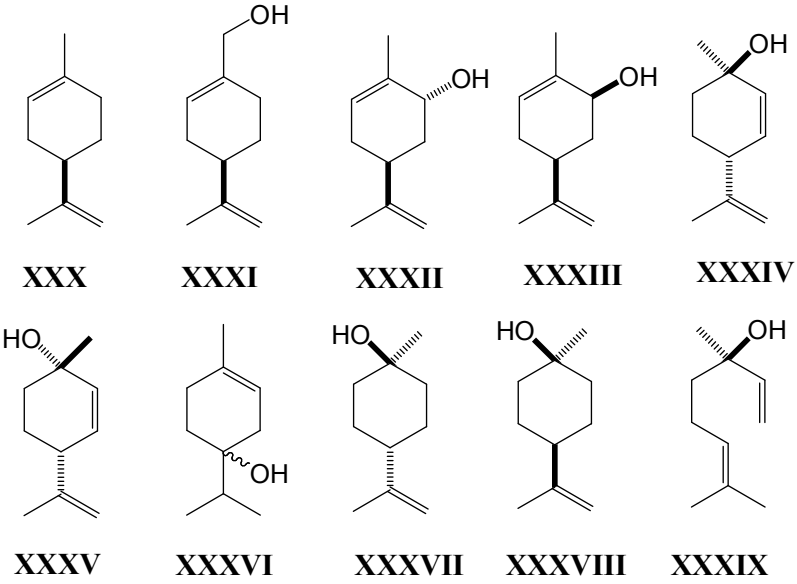
XXVIII



XXIX

(+)-Limonene (**XXX**), a cyclic monoterpene obtained from citrus fruits and many other plants, is metabolized by an *A. niger* strain to perillyl alcohol (**XXXI**) and organic acids (Menéndez et al., 2002). Using two different cultivation systems and two different media, the products include fragrant isomers of *trans*-

carveol (**XXXII**), *cis*-carveol (**XXXIII**), *cis*-*p*-mentha-2,8-dien-1-ol **(XXXIV)**, *trans*-*p*-mentha-2,8-dien-1-ol (**XXXV**), racemic carvone (**XXVII**), perillyl alcohol (**XXXI**), propanoic acid, isobutyric acid, isovaleric acid, the tea tree oil component terpinen-4-ol (**XXXVI**), α-terpineol (**VI**), *cis*-β-terpineol (**XXXVII**), *trans*-β-terpineol (**XXXVIII)**, and the floral scent linalool (**XXXIX**; the (*R*)-(−)-enantiomer is shown) (García-Carnelli et al., 2014):

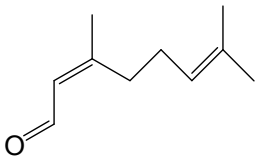


XXX **XXXI** **XXXII** **XXXIII** **XXXIV**

XXXV **XXXVI** **XXXVII** **XXXVIII** **XXXIX**

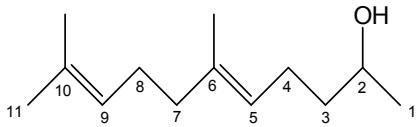
The monoterpenoid alcohol geraniol (**X**), from plant essential oils, is biotransformed by sporulated surface cultures of *A. niger* AN2, mostly to an isomer of linalool (**XXXIX**) with some 6-methyl-5-hepten-2-one. The same strain can also convert the *cis* isomer, nerol (**XII**), or citral, a mixture of the aldehydes geranial

(**XI**) and neral **(XL**), to produce linalool (**XXXIX**) and α-terpineol (**VI**) (Demyttenaere et al., 2000):

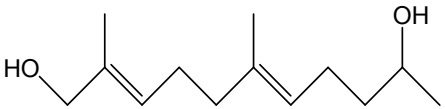


XL

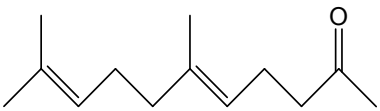
Geranylacetol (**XLI**) is converted by a strain of *A. niger* to 11-hydroxygeranylacetol (**XLII**) and 9,10-dihydroxygeranylacetol, whereas geranylacetone (**XLIII**) is converted to (*S*)-(+)-geranylacetol, 11-hydroxygeranylacetone, and (*S*)-(−)-9,10-dihydroxygeranylacetone, some of which are useful for the synthesis of optically active compounds (Madyastha et al., 1993):



XLI

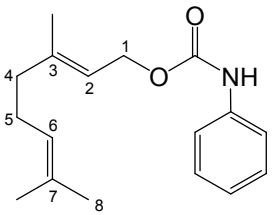


XLII

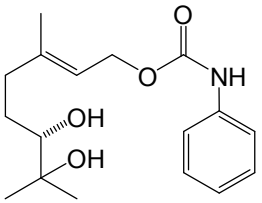


XLIII

The mycelium of *A. niger* LCP 521 hydrolyzes geranyl *N*-phenylcarbamate (**XLIV**) to form (6*R*)-geranyl *N*-phenylcarbamate diol (**XLV**) with an enantiomeric excess over 95% (Fourneron et al., 1989):

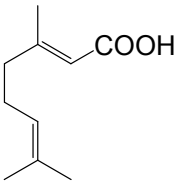


XLIV



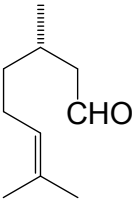
XLV

The bacterium *Rhodococcus* sp. GR3 regioselectively transformed geraniol (**X**) to geranic acid (**XLVI**) in 12.5 h (Chatterjee, 2004):

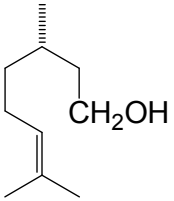


XLVI

The yeast *Rhodotorula minuta* in only 8 h reduced L-(−)-citronellal (**XLVII**) to L-(−)-citronellol (**XLVIII**) with a yield of 78.3% (Velankar and Heble, 2003):

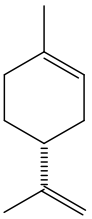


XLVII



XLVIII

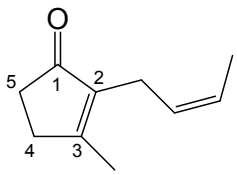
The fungus *Fusarium verticillioides* in 12 h converted R-(+)-limonene (**XLIX**) to R-(+)-perillyl alcohol (**XXXI**) with a yield of 12% (Oliveira and Strapasson, 2000):



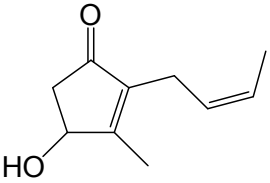
XLIX

Of the microbial transformations of monoterpenoids, those of greatest interest are those producing hydroxylated derivatives (Abraham and Arfmann, 1992; Khor and Uzir, 2011) that can be used in the stereospecific synthesis of valuable compounds, including potential antimalarial drugs.

Cinerone (**L**), a cyclopentenone monoterpenoid, is hydroxylated at the 4-position by *A. niger* ATCC 9142 to produce cinerolone (**LI**), an intermediate in the synthesis of insecticides (Tabenkin et al., 1969):

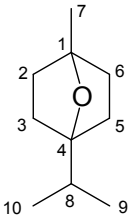


L

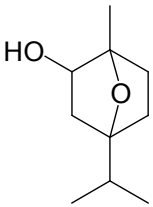


LI

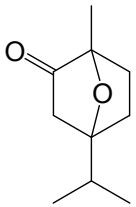
The cyclic ether 1,4-cineole (**LII**) from lime juice is transformed by *A. niger* UI 172 to (±)-2-exo-hydroxy-1,4-cineole (**LIII**), a key precursor in herbicide synthesis, and (±)-2-oxo-1,4-cineole (**LIV**) (Rosazza et al., 1987):



LII

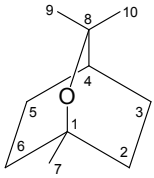


LIII

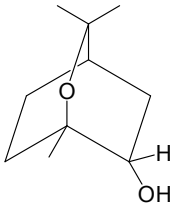


LIV

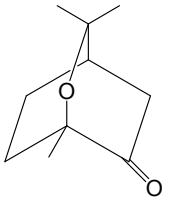
1,8-Cineole (**LV**), also known as eucalyptol, has many uses as a flavoring, fragrance, and insecticide. It is transformed by a strain of *A. niger* to five metabolites, (±)-2-*endo*-hydroxycineole (**LVI**), (±)-2-oxocineole (**LVII**), (±)-3-*endo*-hydroxycineole (**LVIII**), (±)-3-*exo*-hydroxycineole **LIX**), and (±)-3-oxocineole (**LX**). Two of these metabolites, 3-*exo*-hydroxycineole and 3-*endo*-hydroxycineole, are used to synthesize mosquito repellents (Nishimura et al., 1996):



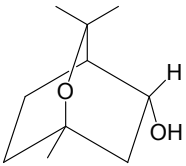
LV



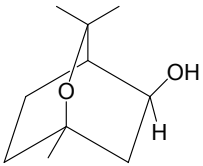
LVI



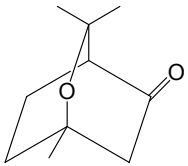
LVII



LVIII

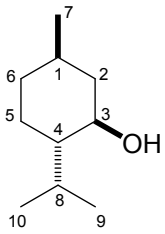


LIX

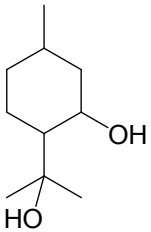


LX

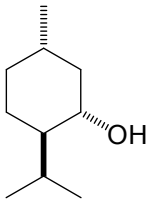
(−)-Menthol (**LXI**), a monoterpenoid flavoring compound from peppermint, is also used as a local anesthetic. It can be biotransformed with a strain of *A. niger* to produce the 1-, 2-, 6-, 7-, 8-, and 9-hydroxymenthols (Asakawa et al., 1991). 8-Hydroxymenthol (**LXII**), also known as *p*-menthane-3,8-diol, is a mosquito repellent. The same strain transforms another isomer, (+)-menthol (**LXIII**), mostly to the 7-hydroxy derivative but also to the 1-, 6-, 8-, and 9-hydroxymenthols (Asakawa et al., 1991):



LXI

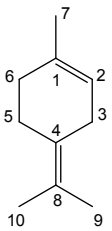


LXII

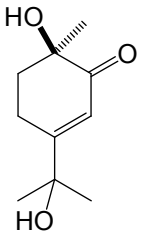


LXIII

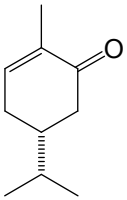
Terpinolene (δ-terpinene, **LXIV**), a monoterpene used for making plastics and resins, is transformed to 1,8-dihydroxy-*p*-menth-3-ene-2-one (**LXV**) and two minor metabolites by the same strain of *A. niger*, which also metabolizes (−)-carvotanacetone (**LXVI**) to *p*-menthane-2,9-diol (**LXVII**) (Asakawa et al., 1991):



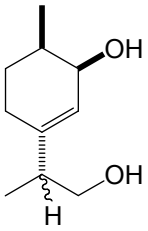
LXIV



LXV

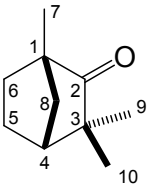


LXVI

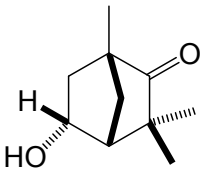


LXVII

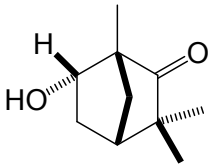
(+)-Fenchone (**LXVIII**), from the essential oil of fennel, is transformed to (+)-5α-hydroxyfenchone (**LXIX**) and (+)-6α-hydroxyfenchone (**LXX**) by a strain of *A. niger* (Noma et al., 1995):



LXVIII



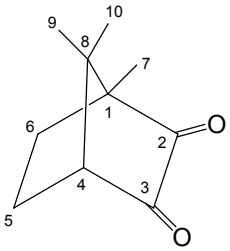
LXIX



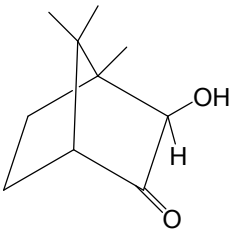
LXX

(+)-Camphorquinone (**LXXI**), used in dental composite resins, is transformed by a strain of *A. niger* mostly to (+)-(2*R*)-*exo*-hydroxyepicamphor (**LXXII**), and (−)-camphorquinone

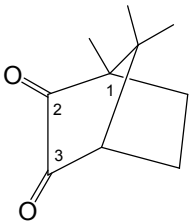
(**LXXIII**) is transformed mostly to (+)-(2*R*)-*endo*-hydroxycamphor (**LXXIV**) (Miyazawa et al., 1995a):



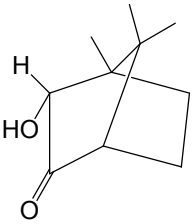
LXXI



LXXII

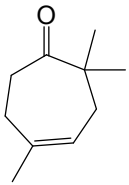


LXXIII

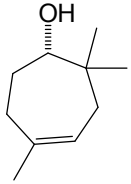


LXXIV

Karahanaenone (**LXXV**), derived from the hop plant, is transformed to a mint aroma compound, (*S*)-karahanaenol (**LXXVI**), by a strain of *A. niger* (Miyazawa et al., 1995b):



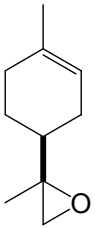
LXXV



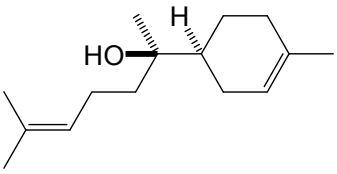
LXXVI

The other enantiomer, (−)-limonene, is also metabolized to carveols and other products by a strain of *A. niger* (Divyashree et al., 2006). The (8*R*) enantiomers in (4*S*,8*RS*)-limonene epoxides

(**LXVII**) and (4*R*,8*RS*)-limonene epoxides, which have two chiral carbons, are hydrolyzed by *A. niger* LCP 521, producing the (4*S*,8*R*) and (4*R*,8*R*) diols, respectively. The (8*S*)-limonene epoxide enantiomers are unchanged by the fungus, so the two epoxides and the two diols can be used in processes to synthesize all four stereoisomers of the sesquiterpenoid alcohol α-bisabolol, including the high-value product (−)-(4*S*,8*S*)-α-bisabolol **(LXVIII)**, for different uses in cosmetics and fragrances (Chen et al., 1993):

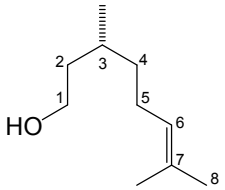


LXVII

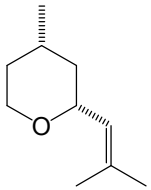


LXVIII

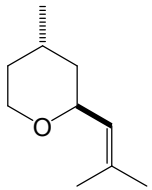
(*R*)-(+)-Citronellol (**LXIX**), an enantiomerically pure monoterpenoid alcohol, is transformed by *A. niger* ANA, mostly to the optical isomers (+)-*cis*-rose oxide (**LXX**) and (+)-*trans*-rose oxide (**LXXI**). In contrast, the isomer (*S*)-(−)-citronellol (**LXXII**) is transformed to (−)-*cis*-rose oxide (**LXXIII**) and (−)-*trans*-rose oxide (**LXXIV**), with 6-methyl-5-hepten-2-one and nerol oxide (**LXXV**) produced as minor metabolites (Demyttenaere et al., 2004):



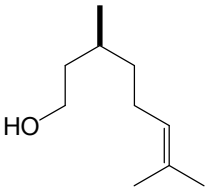
LXIX



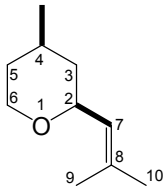
LXX



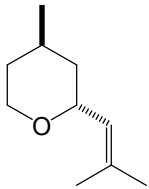
LXXI



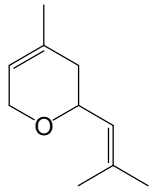
LXXII



LXXIII

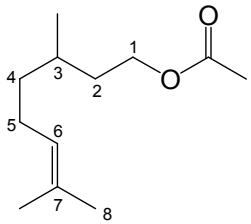


LXXIV



LXXV

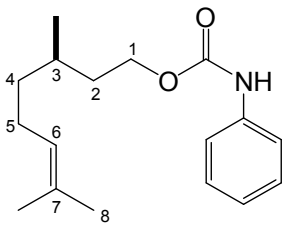
A fragrance ingredient, citronellyl acetate (**LXXVI**), incubated with a strain of *A. niger* produces citronellol (**LXIX**) and 8-hydroxycitronellol**,** with 38 and 60% yield, respectively, in 72 h (Madyastha et al., 1988):



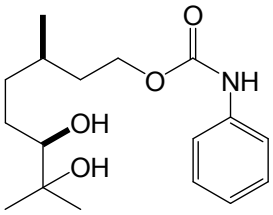
LXXVI

(3*R*)-(+)-Citronellyl *N*-phenylcarbamate (**LXXVII**) is converted by a strain of *A. niger* to either (3*R*,6*R*)-citronellyl *N*-phenylcarbamate diol (**LXXVIII**) or the (3*R*,6*S*)-diol, depending

on the pH; the corresponding (3*S*)-(−)-enantiomer also undergoes similar pH-dependent reactions (Zhang et al., 1992):



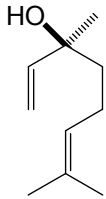
LXXVII



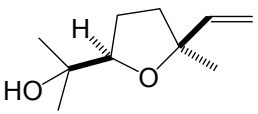
LXXVIII

(−)-*cis*-Rose oxide (**LXX**), a component of the fragrance of roses, is hydroxylated regiospecifically by *A. niger* IFO 4414 in 5 days to (−)-*cis*-9-hydroxy-7*E*-rose oxide, the major product, which may be further oxidized to (−)-*cis*-7*E*-rose oxide-8-carboxylic acid. The analogous (−)-*trans*-metabolites are produced from (−)-*trans*-rose oxide (**LXXI**) (Miyazawa et al., 1995).

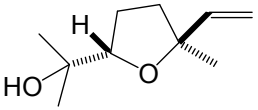
(*S*)-(+)-Linalool (**LXXIX**), one of the isomers of linalool produced by plants, is transformed by *A. niger* DSM 821 to the fragrance ingredients *cis*-(2*S*,5*R*)-furanoid linalool oxide (**LXXX**, yield 30%), *trans*-(2*S*,5*S*)-furanoid linalool oxide (**LXXXI**, yield 5%), and *cis*-(3*S*,6*S*)-pyranoid linalool oxide (**LXXXII**, yield 14%) (Demyttenaere et al., 2001). The other isomer, (*R*)-(−)-linalool (**XXXIX**), is transformed to *trans*-(2*R*,5*R*)-furanoid linalool oxide (**LXXXIII**) and *trans*-(3*S*,6*R*)-pyranoid linalool oxide (**LXXXIV**), but the yields are only 3.3 and 1.1%, respectively (Demyttenaere et al., 2001):



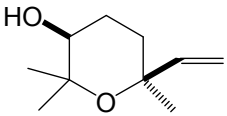
LXXIX



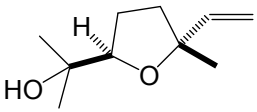
LXXX



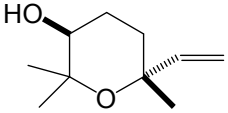
LXXXI



LXXXII

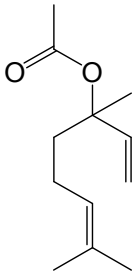


LXXXIII



LXXXIV

Linalyl acetate **(LXXXV)** is metabolized to linalool (**LXXIX**) and 8-hydroxylinalool with 25% and 45% yield, respectively, by a strain of *A. niger*, plus small amounts of geraniol (**X**) and α-terpineol (**VI**) (Madyastha et al., 1988):



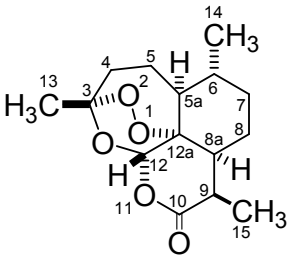
LXXXV

2. Transformation of sesquiterpenoids

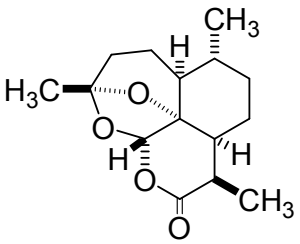
Artemisinin (**LXXXVI**) is the most important antimalarial sesquiterpenoid obtained from plants (Klayman, 1985; Luo and

Shen, 1987; Liao, 2009), although several others have been described (Elmarakby et al., 1987; Chaturvedi et al., 2010; Rustaiyan et al., 2011). Biotransformation of artemisin has been aided by studies of QSAR (quantitative structure-activity relationships), which suggest modifications of artemisinin that are likely to increase antimalarial activity (Avery et al., 2002). Although many terpenoid biotransformations produce metabolites with less antimalarial activity, the products nevertheless may be useful for further modification (Liu et al., 2006). Occasionally, inactive compounds may be transformed to active metabolites by microbial processes (Musharraf et al., 2010).

The bacterium *Nocardia corallina* ATCC 19070 transformed artemisinin to deoxyartemisinin (**LXXXVII**, yield 24%), which lacks antimalarial activity, in 14 days (Lee et al., 1989). Cultures of *Aspergillus flavus* in 48 h transformed artemisinin to deoxyartemisinin (**LXXXVII**) with a yield of 30.5% (Srivastava et al., 2009):

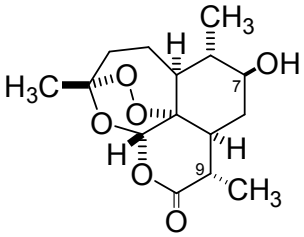


LXXXVI

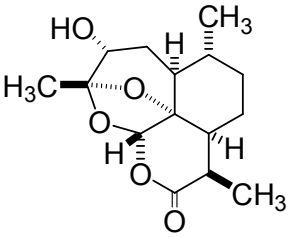


LXXXVII

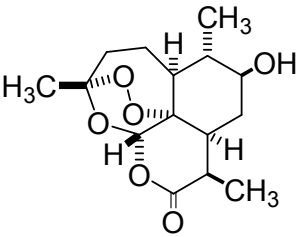
The fungus *Cunninghamella elegans* ATCC 9245 transformed artemisinin to four different hydroxylated derivatives, 7β-hydroxy-9α-artemisinin (**LXXXVIII**, yield 6.0%), 4α-hydroxydeoxyartemisinin (**LXXXIX**, yield 5.4%), 7β-hydroxyartemisinin (**XC**, yield 21.0%) and 6β-hydroxyartemisinin (**XCI**, yield 6.5%). The 7β-hydroxyartemisinin product (**XC**), which cannot be produced chemically, is valuable for further synthesis of candidate antimalarial compounds (Parshikov et al., 2004a, b):



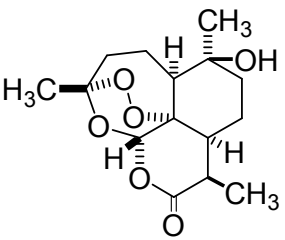
LXXXVIII



LXXXIX



XC



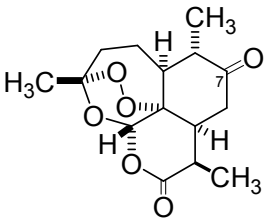
XCI

Penicillium chrysogenum ATCC 9480 transformed artemisinin to two inactive compounds, deoxyartemisinin (**LXXXVII**, yield 1.0%) and 4α-hydroxydeoxyartemisinin (**LXXXIX**, yield 3.6%) in 13 days (Lee et al., 1989). *Cunninghamella echinulata* AS 3.3400 and *Aspergillus niger* AS 3.795 in four days transformed artemisinin to 6β-hydroxyartemisinin (**XCI**, yield 50%) and 4α-hydroxydeoxyartemisinin (**LXXXIX,** yield 15%), respectively (Zhan et al., 2002a), and *Mucor polymorphosporus* AS 3.3443 produced 7β-hydroxyartemisinin (**XC**) and two other hydroxylated products (Zhan et al., 2002b).

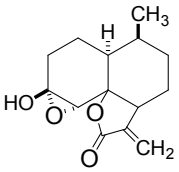
Three strains of *Umbelopsis ramanniana* (*Mucor ramannianus*) hydroxylated artemisinin in 14 days to 7β-hydroxyartemisinin (**XC**, yield 51–88%), 6β-hydroxyartemisinin (**XCI**, yield 1–51%), and two other isomers (Parshikov et al., 2005a, b). *Aspergillus niger* VKM F-1119 hydroxylated artemisinin to 5β-hydroxyartemisinin (yield 80%) and 7β-hydroxyartemisinin (**XC**, yield 19%) (Muraleedharan et al., 2003; Parshikov et al., 2003; 2005c; 2006a, b).

The bacterium *Streptomyces griseus* ATCC 13273 oxidized artemisinin to a less active ketone, artemisitone (**XCII**, yield 12.5%), in 3.5 days (Liu et al., 2006). *Penicillium simplicissimum* modified artemisinin to produce 4β-acetoxy and 4α-hydroxy derivatives (Goswami et al., 2010).

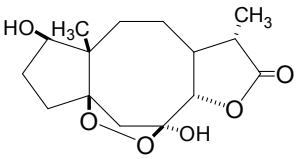
A few other natural sesquiterpenoids have been investigated for possible biotransformations. Arteannuin B (**XCIII**), another terpenoid produced by *Artemisia annua*, is transformed by the fungi *Aspergillus flavipes* and *Beauveria bassiana* to three different products (Elmarakby et al., 1987). A *Microbacterium trichotecenolyticum* extract transformed arteannuin B to artemisinin (Tatineni et al., 2006). Artediffusin (**XCIV**), a recently discovered sesquiterpene lactone produced by *Artemisia diffusa* (Rustaiyan et al., 2011), has antimalarial activity and may also be amenable to biotransformation:



XCII



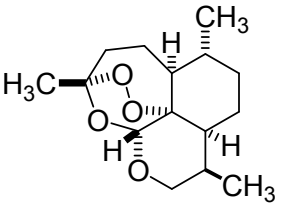
XCIII



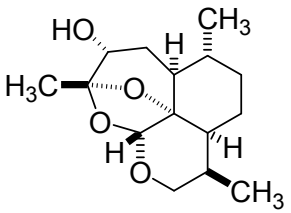
XCIV

Semisynthetic derivatives of artemisinin also have interested researchers seeking possible microbiological modifications. For example, *U. ramanniana* 1839 transformed the semisynthetic antimalarial drug 10-deoxoartemisinin (**XCV**) to the inactive 4α-hydroxydeoxy-10-deoxoartemisinin (**XCVI**, yield 7.0%) and the partially active 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 10.9%) in 14 days (Khalifa et al., 1995). Medeiros et al. (2002) optimized the conditions and obtained a 45% yield of

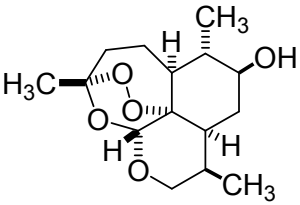
XCVII, which despite its lower antimalarial activity may be useful for further transformations, in 14 days. *Aspergillus niger* hydroxylated 10-deoxoartemisinin (**XCV**) to 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 69%) and 15-hydroxy-10-deoxoartemisinin (yield 26%) (Parshikov et al., 2004a). *Cunninghamella elegans* ATCC 9245 transformed 10-deoxoartemisinin (**XCV**) to three hydroxylated derivatives, 5β-hydroxy-10-deoxoartemisinin (**XCVIII**, yield 8.8%), 4α-hydroxydeoxy-10-deoxoartemisinin (**XCVI**, yield 4.6%) and 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 83.9%) (Parshikov et al., 2004c):



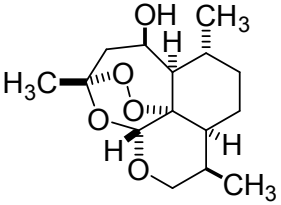
XCV



XCVI



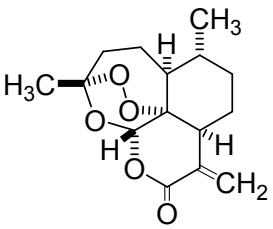
XCVII



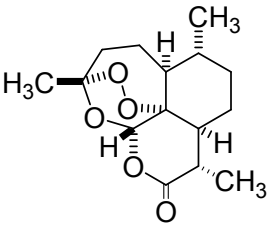
XCVIII

A minor sesquiterpene of *Artemisia annua*, artemisitene (**XCIX**), can also be produced chemically from artemisinin (Chaturvedi et al., 2010). Artemisitene was transformed by *A.*

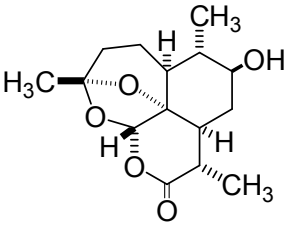
niger NRRL 599 to 9α-artemisinin (**C**), 7β-hydroxydeoxy-9α-artemisinin (**CI**) and 7β-hydroxy-9α-artemisinin (**LXXXVIII**), which has antimalarial activity (Orabi et al., 1999):



XCIX



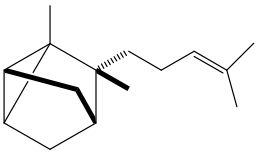
C



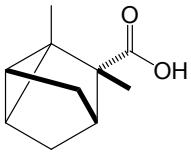
CI

Three isoprene units are used to make up the sesquiterpenoids, many of which have anti-inflammatory and other medicinal properties. Sesquiterpenoid drugs have been used in the treatment of diseases including cancer, cardiovascular disease, and malaria (Bhatti et al., 2009; Huang et al., 2012).

α-Santalene (**CII**), a fragrant sesquiterpene from sandalwood essential oil, is metabolized by a strain of *A. niger*, mostly to the monoterpenoid teresantalic acid (**CIII**), which is used as a flavoring ingredient (Prema et al., 1962):

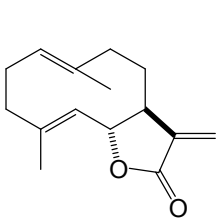


CII

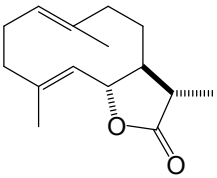


CIII

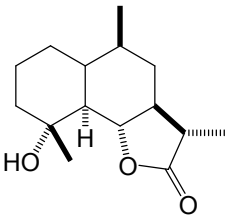
Costunolide (**CIV**), a sesquiterpenoid lactone from magnolia trees that is cytotoxic to tumor cells *in vitro*, is converted *by A. niger* ATCC 16888 to dihydrocostunolide (**CV**), colartin (**CVI**), 11,13-dihydrosantamarine (**CVII**), 11,13-dihydroreynosin (**CVIII**), and tetrahydrovulgarin (**CIX**); all of these metabolites, however, lack cytotoxicity to tumor cells (Clark et al., 1979):



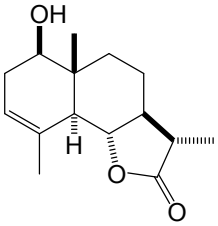
CIV



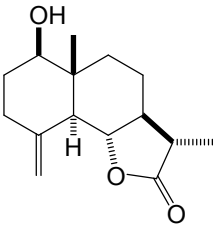
CV



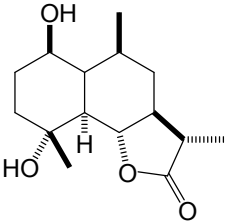
CVI



CVII

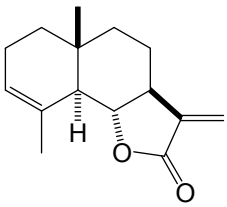


CVIII

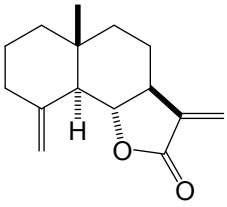


CIX

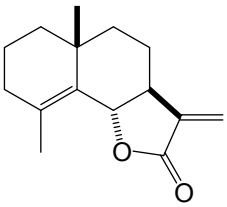
The sesquiterpenoids α-cyclocostunolide (**CX**), β-cyclocostunolide (**CXI**), and γ-cyclocostunolide (**CXII**) are transformed by another strain of *A. niger* by double-bond reduction, hydroxylation, methylene oxidation, and conjugation to form several metabolites (Hashimoto et al., 2001):



CX

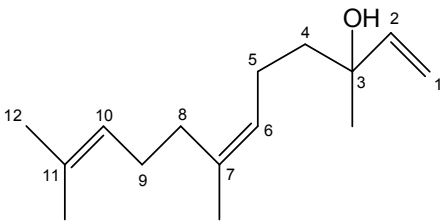


CXI

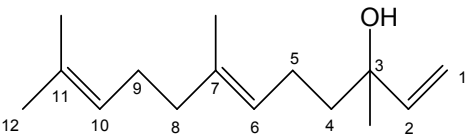


CXII

The nerolidols are sesquiterpenoids from plant essential oils that are used in flavors and perfumes. *cis*-nerolidol (**CXIII**) is transformed by *A. niger* ATCC 9142 to a major product, 10,11-dihydroxy-10,11-dihydro-*cis*-nerolidol, and a minor product, 12-hydroxy-*cis*-nerolidol (Arfmann et al., 1988). *trans*-nerolidol (**CXIV**) is transformed by the same strain to all-*trans*-12-hydroxynerolidol, 10,11-dihydroxy-10,11-dihydro-*trans*-nerolidol, 1,2,12-trihydroxy-1,2-dihydro-*trans*-nerolidol, *trans*-nerolidol 12-carboxylic acid, *trans*-12-acetoxynerolidol, and 6*E*,10*Z*-12-hydroxynerolidol (Arfmann et al., 1988):

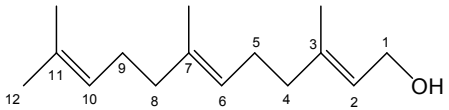


CXIII

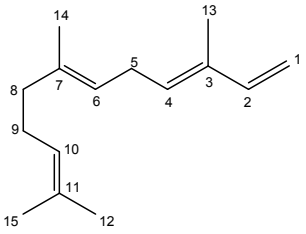


CXIV

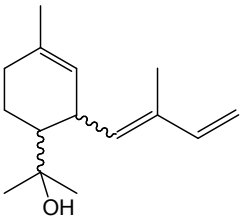
Farnesol (**CXV**), a sesquiterpenoid alcohol from plant essential oils, is used in perfumes, tobacco flavoring, and pesticides. A mixture of farnesol isomers is hydroxylated by *A. niger* DSM 63263 to produce 12-hydroxyfarnesol (Arfmann et al., 1988); and by another strain of *A. niger* to produce 12-hydroxyfarnesol (yield 35%) and 10,11-dihydroxyfarnesol (yield 48%) [33]. α-Farnesene (**CXVI**), a sesquiterpene found in the essential oils of fruits, is transformed by *A. niger* LB 2025 to four terpenoid alcohols: two diastereomers of *p*-menth-1-en-3-[2-methyl-1,3-butadienyl]-8-ol (**CXVII**) and two diastereomers of 2,6,10-trimethyldodeca-2,7,9,11-tetraen-6-ol (Krings et al., 2006):



CXV

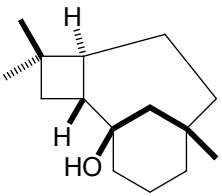


CXVI

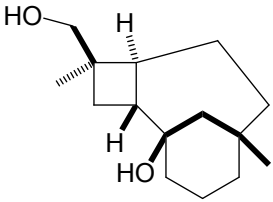


CXVII

(*R*)-Caryolan-1-ol (**CXVIII**) is transformed by *A. niger* MMP 521, forming caryolan-1,14-diol (**CXIX**) with a yield of 26% (Lamare et al., 1989):

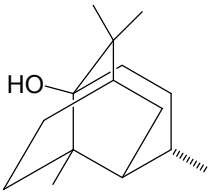


CXVIII

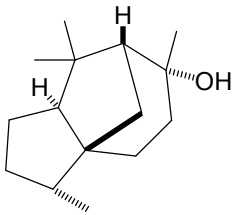


CXIX

The fragrance compound patchoulol (**CXX**), from patchouli oil, is hydroxylated by a strain of *A. niger* to form a diol (Lamare et al., 1990). Cedrol (**CXXI**), from cedarwood oil, is hydroxylated by *A. niger* ATCC 9142 to form another diol (Lamare et al., 1990):

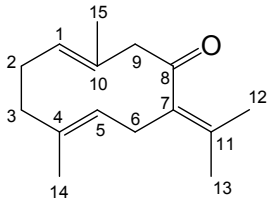


CXX

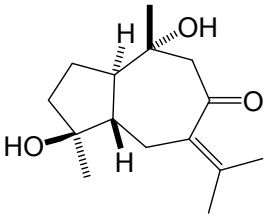


CXXI

Germacrone (**CXXII**), a sesquiterpenoid produced by several plants, is transformed by a strain of *A. niger* to the anti-inflammatory drug zedoarondiol (**CXXIII**) and 3β-hydroxygermacrone (Asakawa et al., 1991; Cho et al., 2009):

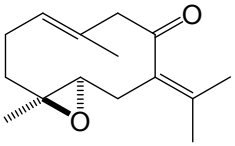


CXXII

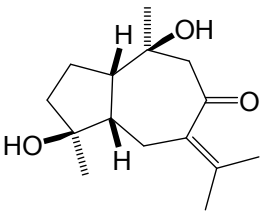


CXXIII

(+)-Germacrone-4,5-epoxide (**CXXIV**), a sesquiterpenoid epoxide derived from a species of turmeric, is transformed by a strain of *A. niger* into zedoarondiol (**CXXIII**) and isozedoarondiol (**CXXV**) (Asakawa et al., 1991):

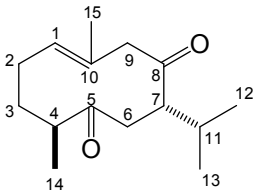


CXXIV

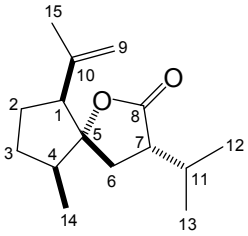


CXXV

(+)-Curdione (**CXXVI**), from a traditional Chinese medicine, is transformed by growing cells of *A. niger* AS 3.739 to several metabolites, including 3α-hydroxycurdione, 2β-hydroxycurdione, curcumalactone (**CXXVII**), 3α-hydroxycurcumalactone, (10*S*)-9,10-dihydroxycurcumalactone, and (10*R*)-9,10-dihydroxycurcumalactone (Asakawa et al., 1991; Chen et al., 2014):

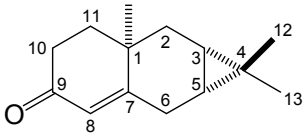


CXXVI



CXXVII

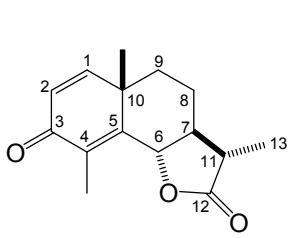
A sesquiterpenoid ketone, 1,4,4-trimethyltricyclo[5.4.0.0^{3,5}]undec-7-en-9-one (**CXXVIII**), is hydroxylated at the 13- and 12-methyl groups by *A. niger* ATCC 9142 to produce 4(*S*)- and 4(*R*)-(hydroxymethyl)-1,4-dimethyltricyclo[5.4.0.0^{3,5}]undec-7-en-9-one, respectively (Hebda et al., 1991):



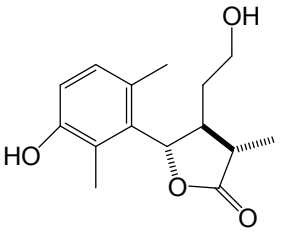
CXXVIII

(−)-α-Santonin (**CXXIX**), a sesquiterpenoid lactone from the sandalwood plant, was formerly used as an anthelmintic. It is transformed by one strain of *A. niger* to 1,2-dihydro-α-santonin (Atta-ur-Rahman et al., 1998) and by a different strain to 1-hydroxy-α-santonin, 13-hydroxy-α-santonin, 3,6,9-trihydroxy-9,10-*seco*-selina-1,3,5(10)-trien-12-oic acid-12,6-lactone (**CXXX**), and the photoproduct lumisantonin (**CXXXI**) (Hashimoto et al., 2001). Another strain, *A. niger* ATCC 9142, transforms (−)-α-

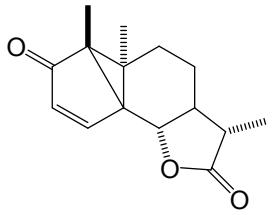
santonin (**CXXIX**) to 11β-hydroxy-α-santonin, 14-hydroxy-α-santonin, and 3,6-dihydroxy-9-keto-9,10-*seco*-selina-1,3,5(10)-trien-12-oic acid-12,6-lactone (**CXXXII**) (Lamm et al., 2009):



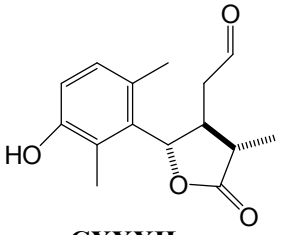
CXXIX



CXXX



CXXXI

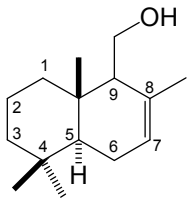


CXXXII

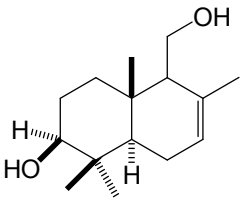
11,13-Dehydro-(−)-α-santonin is transformed by *A. niger* MIL 5024 to produce the metabolites (−)-α-santonin (**CXXIX**), 11β-hydroxy-(−)-α-santonin, 13-hydroxy-(−)-α-santonin, 3,6,9-trihydroxy-9,10-*seco*-selina-1,3,5(10)-trien-l2-oic acid-12,6-lactone (**CXXX**), and 8β-hydroxy-(−)-α-santonin (Iida et al., 1993).

(−)-Drimenol (**CXXXIII**), a sesquiterpenoid alcohol from the Winter's bark tree of Chile and Argentina, is useful for chiral synthesis. Hydroxylation by a strain of *A. niger* produces 3β-hydroxy-(−)-drimenol (**CXXXIV**); drimenyl acetate (**CXXXV**) is

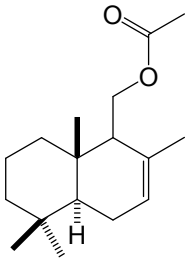
also transformed to the corresponding 3β-hydroxy derivative (Ramirez et al., 1993):



CXXXIII

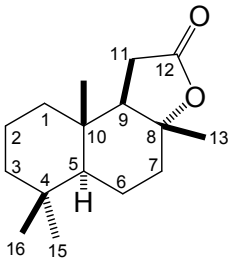


CXXXIV



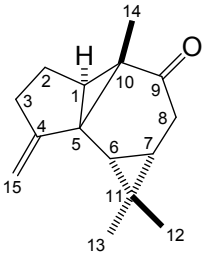
CXXXV

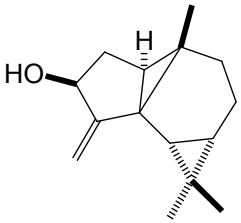
Sclareolide (**CXXXVI**), a sesquiterpenoid lactone obtained from sage plants and used as a fragrance, is transformed by *A. niger* ATCC 10549 to five metabolites: 3-ketosclareolide, 1β- and 3β-hydroxysclareolide, and 1α,3β- and 1β,3β-dihydroxysclareolide (Atta-ur-Rahman et al., 1997):



CXXXVI

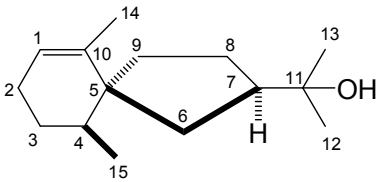
Myli-4(15)-en-9-one (**CXXXVII**) and myliol (**CXXXVIII**), two sesquiterpenoids derived from a liverwort, are hydroxylated by *A. niger* IFO 4407 at the 12-methyl group (Hayashi et al., 1998):





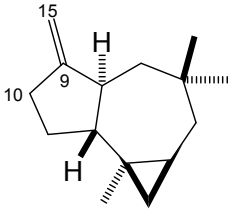
CXXXVII **CXXXVIII**

(−)-Hinesol (**CXXXIX**), a sesquiterpenoid alcohol from a Chinese medicinal plant, is transformed by a strain of *A. niger* to eight metabolites: 2-ketohinesol, 2α- and 2β-hydroxyhinesol, two *trans*-1,2-dihydrodiols, 3α,13- and 3α,12-dihydroxyhinesol 10,11-ethers, and 3α,13-dihydroxy-1,2-epoxyhinesol 10,11-ether (Hashimoto et al., 1999):



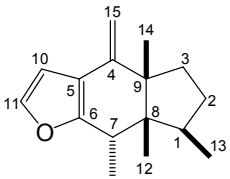
CXXXIX

The tricyclic sesquiterpene $\Delta^{9(15)}$-africanene (**CXL**), incubated with *A. niger* ATCC 9642 for 8 days, produces 10α-hydroxy-$\Delta^{9(15)}$-africanene and 9α,15-epoxyafricanane (Venkateswarlu et al., 1999):

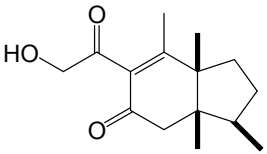


CXL

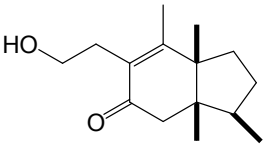
Dehydropinguisenol (**CXLI**), a furanosesquiterpenoid alcohol obtained from a liverwort, is metabolized by a strain of *A. niger* to two metabolites, 10-oxolejeuneapinguisenol (**CXLII**) and lejeuneapinguisenol (**CXLIII**), in 3 to 5 days of incubation (Lahlou et al., 2000):



CXLI

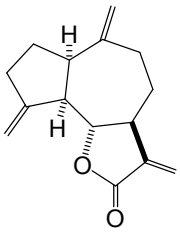


CXLII

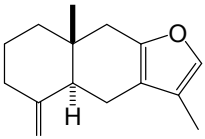


CXLIII

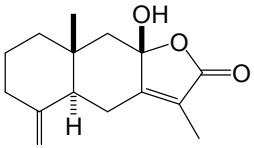
Dehydrocostus lactone (**CXLIV**), a drug derived from an Asian plant, inhibits the activation of NF-κB, a protein complex which regulates immune responses. It is transformed regio- and stereospecifically by a strain of *A. niger* via double-bond reduction, epoxidation, ring hydroxylation, and epoxide hydrolysis to six metabolites (Hashimoto et al., 2001. Atractylon (**CXLV**), found in a Chinese herbal medicine, is transformed by the same strain to produce atractylenolide III (**CXLVI**), which inhibits vascular permeability (Hashimoto et al., 2001):



CXLIV

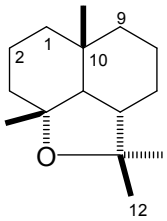


CXLV



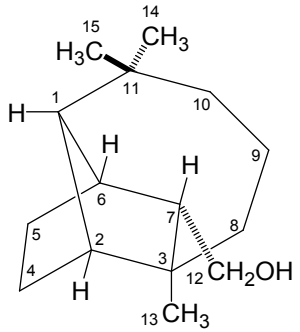
CXLVI

A sesquiterpenoid cyclic ether from a liverwort, (−)-maalioxide (**CXLVII**), is hydroxylated by a strain of *A. niger* to three metabolites: 1β-hydroxy-(−)-maalioxide, 1β,9β-dihydroxy-(−)-maalioxide, and 1β,12-dihydroxy-(−)-maalioxide (Hashimoto et al., 2004):



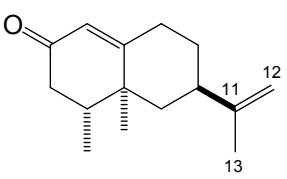
CXLVII

(−)-Isolongifolol (**CXLVIII**), a derivative of a sesquiterpene from Himalayan pine resin, is transformed by *A. niger* ATCC 10549 to the metabolites 10α- and 9α-hydroxyisolongifolol, which inhibit butyrylcholinesterase activity and have been investigated for the treatment of diseases of the nervous system (Choudhary et al., 2005):

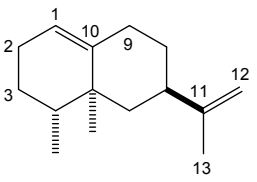


CXLVIII

Nootkatone (**CXLIX**), a sesquiterpenoid ketone from grapefruits, is biotransformed by a strain of *A. niger* to three metabolites, 12-hydroxy-11,12-dihydronootkatone (yield 10.6%) and a mixture of (11*R*)- and (11*S*)-nootkatone-11,12-diol (combined yield 51.5%) (Furusawa et al., 2005). The related sesquiterpene valencene (**CL**), from orange oil, can be biotransformed by the same strain to the same three metabolites as nootkatone plus four minor metabolites. The ratio of (11*R*)- and (11*S*)-diols from valencene was found by derivatization and HPLC analysis to be 3:1 (Furusawa et al., 2005):

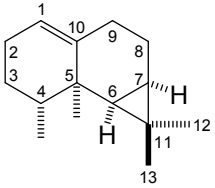


CXLIX

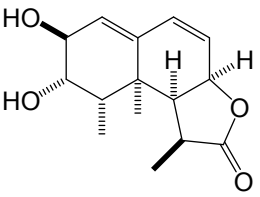


CL

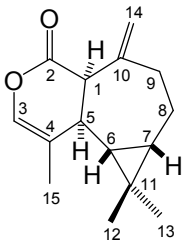
A tricyclic sesquiterpene, (+)-1(10)-aristolene (**CLI**), from a Chinese medicinal plant, is transformed by a strain of *A. niger* to 2-oxo-1(10)-aristolen-12-oic acid, 3β-hydroxy-1(2),9(10)-aristoladien-13-oic acid, 3-oxo-1(2),9(10)-aristoladien-13-oic acid, and 2β,3α-dihydroxynardosinan-1(10),8(9)-dien-11β-methyl-12,7-olide (**CLII**) (Furusawa et al., 2006). The same strain also transforms plagiochilide (**CLIII**), a sesquiterpenoid from a liverwort, to 12-hydroxyplagiochilide and plagiochilid-12-oic acid (Furusawa et al., 2006):



CLI

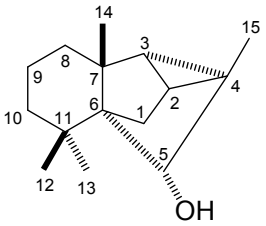


CLII

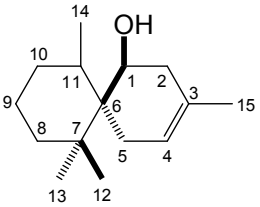


CLIII

Cyclomyltaylan-5α-ol (**CLIV**), another sesquiterpenoid from a liverwort, is biotransformed by a strain of *A. niger* in 5 days to four metabolites: cyclomyltaylane-5α,9β-diol, cyclomyltaylane-5α,10β-diol, cyclomyltaylane-5α,9β,15-triol, and 5-oxocyclomyltaylane-9β,15-diol (Furusawa et al., 2006). *ent*-β-Chamigren-1β-ol (**CLV**) is transformed to β-chamigren-1β,9α-diol, β-chamigren-1β,8α-diol, and β-chamigren-1β,8α,15-triol (Furusawa et al., 2006):

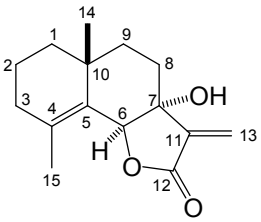


CLIV



CLV

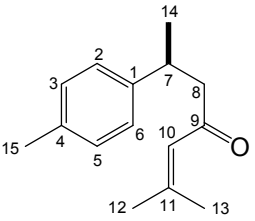
7α-Hydroxyfrullanolide (**CLVI**), a sesquiterpenoid lactone from the East Indian globe thistle, inhibits growth of Gram-positive bacteria and the production of pro-inflammatory cytokines. *A. niger* ATCC 1004 transforms it to three metabolites: 11,13-dihydro-7α-hydroxyfrullanolide, 13-acetyl-7α-hydroxyfrullanolide, and 2α,7α-dihydroxyfrullanolide, which are much less antibacterial (Ata et al., 2009):



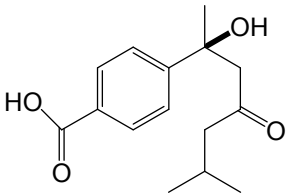
CLVI

A sesquiterpenoid, (+)-(*S*)-*ar*-turmerone (**CLVII**), from the rhizomes of black turmeric, inhibits acetylcholinesterase activity. It is oxidized by *A. niger* NBRC 4414 to four metabolites: (+)-(7*S*)-hydroxydehydro-*ar*-todomatuic acid (**CLVIII**), (+)-(7*S*,10*E*)-

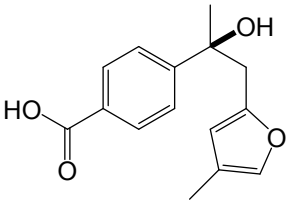
12-hydroxydehydro-*ar*-todomatuic acid, (+)-(7*S*,10*E*)-7,12-dihydroxydehydro-*ar*-todomatuic acid, and (+)-(7*S*)-15-carboxy-9,13-epoxy-7-hydroxy-9,13-dehydro-*ar*-curcumene (**CLIX**) (Fujiwara et al., 2011). The same strain also metabolizes (+)-(*S*)-dihydro-*ar*-turmerone (**CLX**) to (+)-7,11-dihydroxy-*ar*-todomatuic acid (Fujiwara et al., 2011):



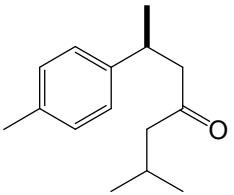
CLVII



CLVIII

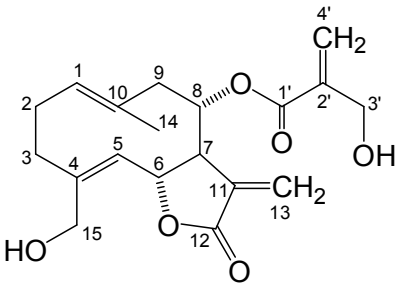


CLIX



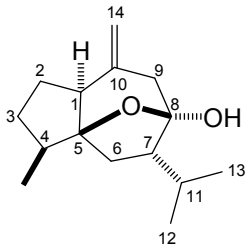
CLX

Onopordopicrin (**CLXI**), an antibacterial but cytotoxic sesquiterpenoid lactone produced by several plants, is transformed by *A. niger* PTCC 5011 to 11αH-dihydroonopordopicrin, 11βH-dihydroonopordopicrin, 3β-hydroxy-11βH-dihydroonopordopicrin, and 14-hydroxy-11βH-dihydroonopordopicrin (Esmaeili et al., 2012):

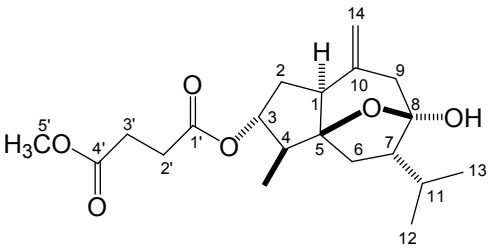


CLXI

Curcumol (**CLXII**), a sesquiterpenoid with antitumor and antivirus activity, is derived from a species of turmeric used in Chinese traditional medicine. It is transformed by *A. niger* AS 3.739 to 3α-hydroxycurcumol and 3α-(4'methoxysuccinyloxy)-curcumol (**CLXIII**) (Chen et al., 2013):

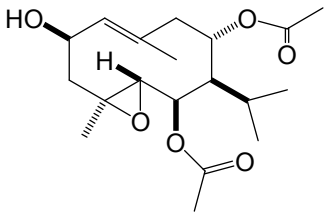


CLXII



CLXIII

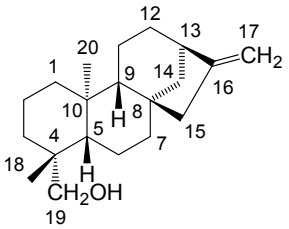
Shiromodiol diacetate, a sesquiterpenoid epoxide obtained from an Asian tree, is hydroxylated by *A. niger* IFO 4407 to produce 2β-hydroxyshiromodiol diacetate (**CLXIV**), with a 59% yield in 4 days (Hayashi et al., 1998):



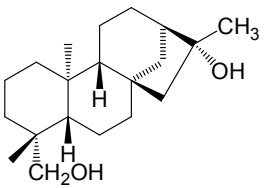
CLXIV

3. Transformation of diterpenoids

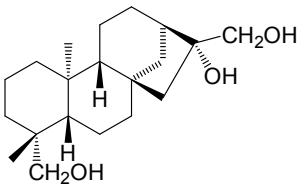
Many diterpenoids from medicinal plants have antimalarial activity (García et al., 2007; Titanji et al., 2008; Kaur et al., 2009). Cultures of the fungus *Cephalosporium aphidicola* CCT 2163 hydroxylate the kaurane diterpenoid *ent*-kaur-16-en-19-ol (**CLXV**) with formation of two products, *ent*-kauran-16b,19-diol (**CLXVI**, yield 54%) and *ent*-kauran-16b,17,19-triol (**CLXVII**, yield 18.6%), in 13 days (Rocha et al., 2009):



CLXV

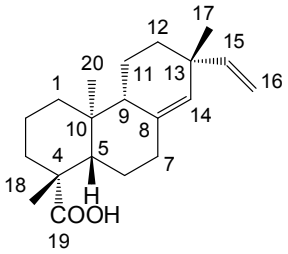


CLXVI

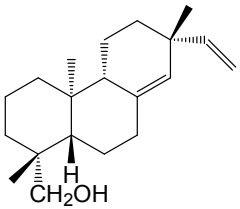


CLXVII

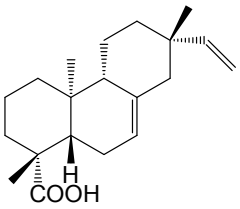
Because plants containing pimarane diterpenoids, such as *Kaempferia marginata*, have been used as antimalarials in traditional medicine, the pimaranes have also been investigated for antimalarial activity (Thongnest et al., 2005). Although the reduction of specific carboxyl groups to alcohols is not always possible by chemical methods, the fungus *Glomerella cingulata* regioselectively transformed *ent*-pimara-8(14),15-dien-19-oic acid (**CLXVIII**) to *ent*-8(14),15-pimaradien-19-ol (**CLXIX,** yield 18.3%) in 10 days (Severiano et al., 2010). *Mucor rouxii* converted **CLXVIII** to *ent*-pimara-7,15-dien-19-oic acid (**CLXX**, yield 2.8%) and 7-keto-*ent*-pimara-8,15-dien-19-oic acid (**CLXXI**, yield 2.1%) in 7 days (Severiano et al., 2010):



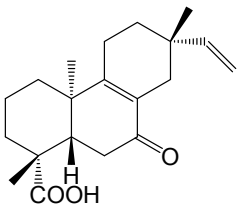
CLXVIII



CLXIX

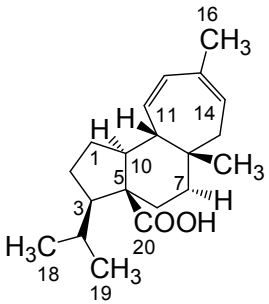


CLXX

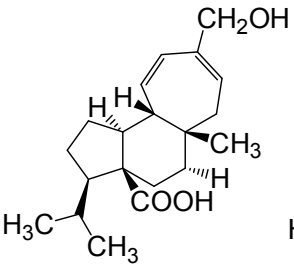


CLXXI

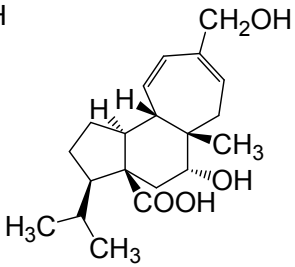
Some mulinane derivatives from the medicinal plant *Azorella compacta* have been shown to have antiplasmodial activity (Loyola et al., 2004). *Mucor plumbeus* IMI 116688 transformed mulin-11,13-dien-20-oic acid (**CLXXII**) to two metabolites, 16-hydroxymulin-11,13-dien-20-oic acid (**CLXXIII**, yield 0.8%) and 7α,16-dihydroxymulin-11,13-dien-20-oic acid (**CLXXIV**, yield 0.75%) in 15 days (Areche et al., 2008):



CLXXII



CLXXIII

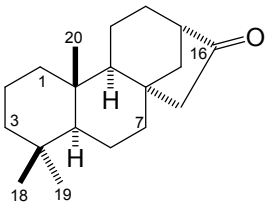


CLXXIV

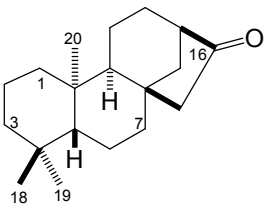
The diterpenoids found in plant resins consist of four isoprene units in a variety of arrangements. They are not used as fragrances, but several of them have medicinal properties, especially the taxoids produced by yew trees, which have valuable anticancer activity. Biotransformation processes have been developed for many diterpenoids (Bhatti et al., 2014).

17-Norkauran-16-one (**CLXXV**) and *ent*-17-norkauran-16-one (**CLXXVI**), which are tetracyclic diterpenoids that are

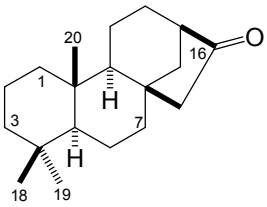
possible gibberellin precursors in plants, are biotransformed by *A. niger* ATCC 26693 to the 3β-hydroxy and 3α-hydroxy derivatives, respectively (Anderson et al., 1975). In contrast, 17-norphyllocladan-16-one (**CLXXVII**) is biotransformed to the 3β-hydroxy and the 3-keto derivatives (Anderson et al., 1975):



CLXXV

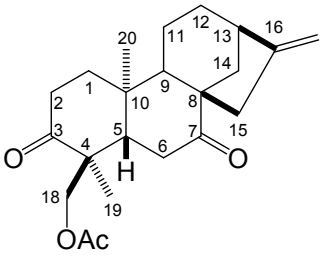


CLXXVI

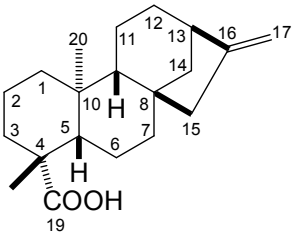


CLXXVII

A similar diterpenoid, *ent*-18-acetoxykaur-16-en-3,7-dione (**CLXXVIII**), can be transformed by *A. niger* CECT 2091. Acetoxyl hydrolysis produces *ent*-18-hydroxykaur-16-en-3,7-dione in 2 days; *ent*-16β,18- and *ent*-17,18-dihydroxykauran-3,7-dione; and *ent*-l6α,17,18- and *ent*-16β,17,18-trihydroxykauran-3,7-dione can also be isolated after 6 days (García-Granados et al., 1986). *ent*-Kaur-16-en-19-oic acid (kaurenoic acid, **CLXXIX**), a diterpenoid from the roots of a medicinal plant, has antispasmodic and anti-inflammatory properties. It is transformed by *A. niger* AN-1 to two dihydroxylated metabolites, *ent*-7α,11β-dihydroxy-kaur-16-en-19-oic acid (20% yield) and *ent*-1β,7α-dihydroxy-kaur-16-en-19-oic acid (5.8% yield) in 13 days (Marquina et al., 2009):

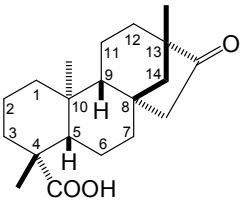


CLXXVIII

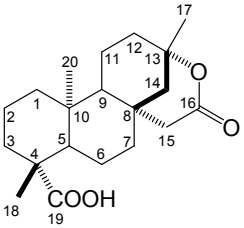


CLXXIX

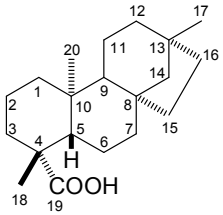
Isosteviol (**CLXXX**), an *ent*-beyer-19-oic acid derivative with a variety of biological effects, is biotransformed by *A. niger* CMI 17454 to form 7β-hydroxyisosteviol and 1α,7β-dihydroxyisosteviol (Oliveira et al., 1999). Another strain, *A. niger* IFO 4414, metabolizes isosteviol not only to 7β-hydroxyisosteviol but also to 11β- and 12β-hydroxyisosteviol; all three of these metabolites have antitumor activity (Akihisa et al., 2004). Isosteviol lactone (**CLXXXI**) is biotransformed by *A. niger* BCRC 31130 to seven different hydroxylated diterpenoids, some of which inhibit the activator protein-1 transcription factor (Chou et al., 2009). Isostevic acid (**CLXXXII**) is hydroxylated by *A. niger* BCRC 32720 to eight metabolites with anti-inflammatory properties (Yang et al.,2012):



CLXXX

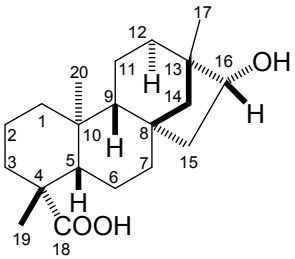


CLXXXI

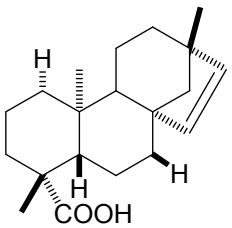


CLXXXII

The tetracyclic diterpenoid *ent*-16β-hydroxybeyeran-19-oic acid (**CLXXXIII**) is hydroxylated by *A. niger* CCRC 32720 to *ent*-1β,7α,16β-trihydroxybeyeran-19-oic acid and *ent*-1β,7α-dihydroxy-16-oxobeyeran-19-oic acid, both of which have greater antihypertensive activity than the starting drug [81]. A similar diterpenoid from a Mexican plant, *ent*-beyer-15-en-19-oic acid (**CLXXXIV**), is hydroxylated by *A. niger* AN-1 to *ent*-1β,7α-dihydroxy-beyer-15-en-19-oic acid (yield 40%) (Marquina et al., 2009):



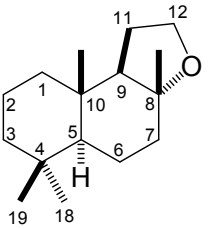
CLXXXIII



CLXXXIV

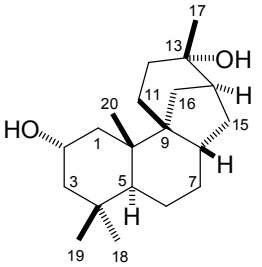
(−)-Ambroxide (Ambrox, **CLXXXV**), a diterpenoid used in fragrances, is transformed by a strain of *A. niger*, by oxidation at

the C3 and C18 positions and hydrolysis of the furan ring, to produce four metabolites (Hashimoto et al., 2001):

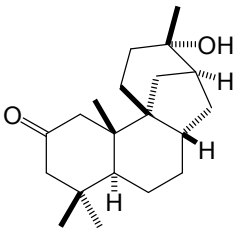


CLXXXV

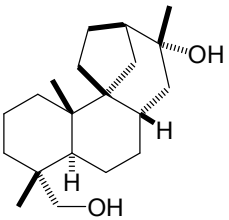
Stemodin (**CLXXXVI**), a tetracyclic diterpenoid produced by the seaside twintip plant of Jamaica, is biotransformed in cultures of *A. niger* ATCC 9142 to 2α,3β,13-, 2α,7β,13-, and 2α,13,16β-trihydroxystemodane (Furusawa et al., 2005). The same strain also transforms stemodinone (**CLXXXVII**) to 13,18- and 13,16β-dihydroxystemodan-2-one; and it transforms stemarin (**CLXXXVIII**) to four metabolites, including three carboxylic acids (Chen et al., 2002):



CLXXXVI

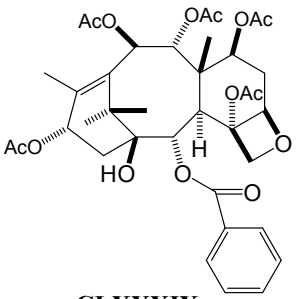


CLXXXVII

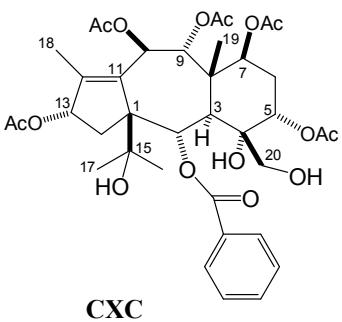


CLXXXVIII

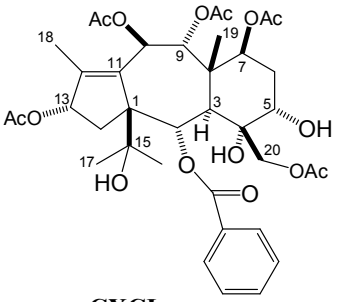
Baccatin VI (**CLXXXIX**), a taxoid diterpenoid from a Chinese yew tree, can be biotransformed with *A. niger* BCRC 31130 to produce the diterpenoids taxumairol S_1 (**CXC**) and taxumairol T_1 (**CXCI**), which have been used in antitumor research (Shen et al., 2003):



CLXXXIX

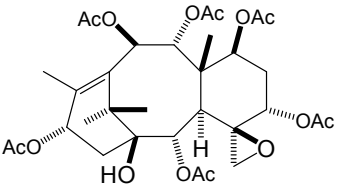


CXC

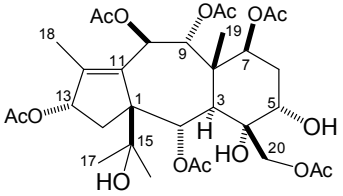


CXCI

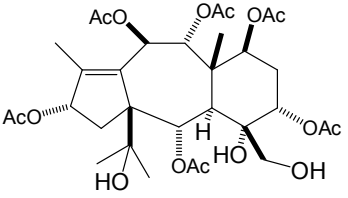
Similarly, the biotransformation of 1β-hydroxybaccatin I (**CXCII**), a polyacetylated diterpenoid epoxide from the Chinese yew, by *A. niger* BCRC 31130 produces a mixture of taxumairol S (**CXCIII**) and taxumairol T (**CXCIV**) (Shen et al., 2003):



CXCII

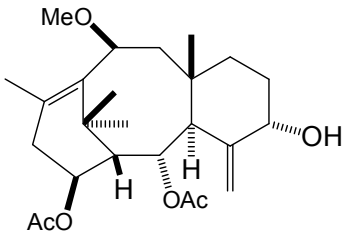


CXCIII



CXCIV

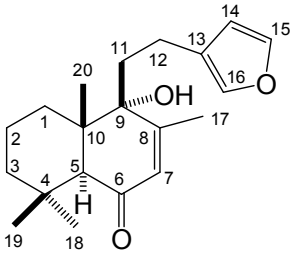
5α-Hydroxy-10β-methoxy-2α,14β-diacetoxytaxa-4(20),11(12)-diene (**CXCV**), a taxadiene diterpenoid, is transformed by *A. niger* CGMCC 3.1858 by demethylation, acetylation, deacetylation, and O-alkylation to seven metabolites. One of them, 2α-hydroxy-5α,10β,14β-triacetoxytaxa-4(20),11(12)-diene, has the potential to prevent resistance to chemotherapeutic drugs in some tumor cells (Liu et al., 2012):



CXCV

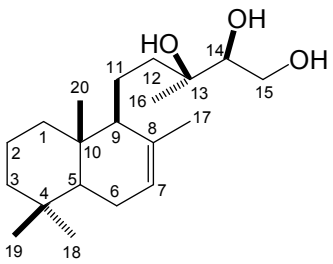
Solidagenone (**CXCVI**), a diterpenoid found in Chilean goldenrod rhizomes, is hydroxylated to 3β-hydroxy- and 19-

hydroxysolidagenone, which have gastroprotective effects on cultured epithelial cells, when incubated with *A. niger* ATCC 16404 (Schmeda-Hirschmann et al., 2004):

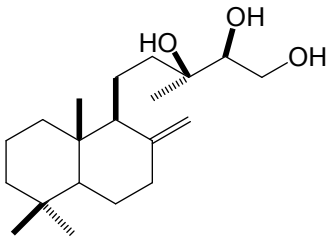


CXCVI

A diterpenoid from a tarweed plant, 13*R*,14*R*,15-trihydroxylabd-7-ene (**CXCVII**), is transformed by a strain of *A. niger* to produce 3β,13*R*,14*R*,15-tetrahydroxy-labd-7-ene; and 13*R*,14*R*,15-trihydroxylabd-8(17)-ene (**CXCVIII**) is transformed by the same strain to produce 7α,13*R*,14*R*,15-tetrahydroxylabd-8(17)-ene and 13*R*,14*R*,15-trihydroxy-3-oxo-labd-8(17)-ene (Haridy et al., 2006):

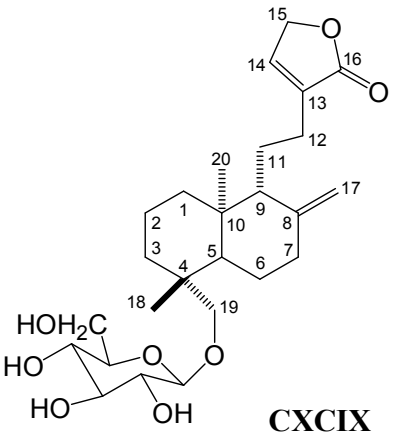


CXCVII



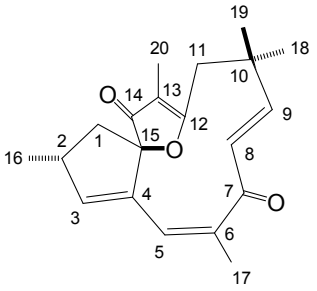
CXCVIII

Neoandrographolide (**CXCIX**), a diterpenoid from a Chinese traditional medicinal plant, is biotransformed by *A. niger* AS 3.739 to five products: 8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, 19-hydroxy-8(17),13-*ent*-labdadien-16,15-olide, 18-hydroxy-8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, 3α-hydroxy-8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, and 8β,19-dihydroxy-*ent*-labd-13-en-16,15-olide (Chen et al., 2007):

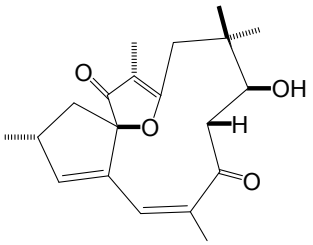


CXCIX

Jatrophone (**CC**), a relatively toxic antiprotozoal and antileukemic diterpenoid from a plant native to Middle and South America, is regioselectively converted by *A. niger* ATCC 16404 to a small amount of the much less cytotoxic 9β-hydroxyisabellione in 25 days (**CCI**, yield 0.65%) (Pertino et al., 2007):

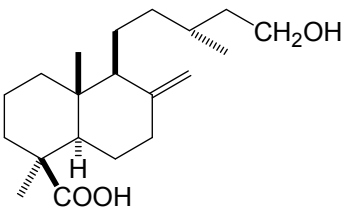


CC

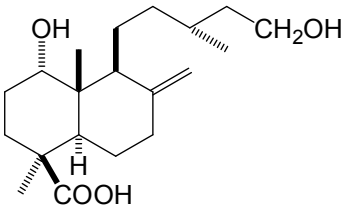


CCI

Imbricatolic acid (**CCII**), a diterpenoid obtained from the common juniper, is regioselectively transformed by cultures of *A. niger* ATCC 16404 to 1α-hydroxyimbricatolic acid (**CCIII**) in 15 days (Schmeda-Hirschmann et al., 2007):

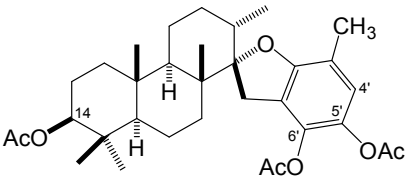


CCII

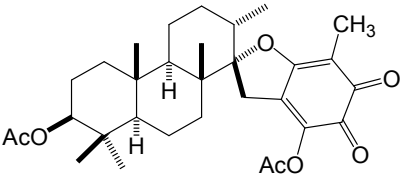


CCIII

Stypotriol triacetate (**CCIV**), a derivative of a compound found in brown algae, is converted by *A. niger* ATCC 16404 to 6',14-diacetoxystypol-4',5'-dione (**CCV**) in 20 days, with a 1.7% yield after purification (Areche et al., 2011):

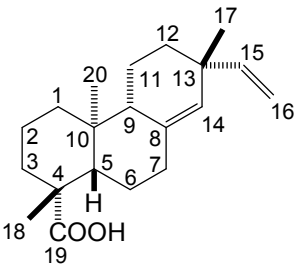


CCIV



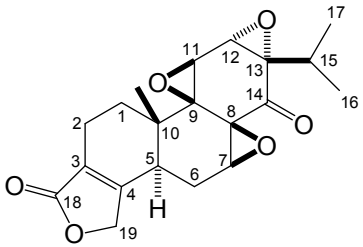
CCV

ent-Pimaradienoic acid (**CCVI**), an antibacterial diterpenoid from a Chinese yew tree, is derivatized by biotransformation with a strain of *A. niger* to 7α-hydroxy-*ent*-pimara-8(14),15-dien-19-oic acid, 1β-hydroxy-*ent*-pimara-6,8(14),15-trien-19-oic acid, 1α,6β,14β-trihydroxy-*ent*-pimara-7,15-dien-19-oic acid, and 1α,6β,7α,11α-tetrahydroxy-*ent*-pimara-8(14),15-dien-19-oic acid (Severiano et al., 2013):



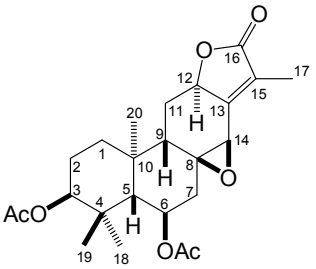
CCVI

Triptonide (**CCVII**), a diterpenoid triepoxide lactone from a Chinese medicinal vine, has anti-inflammatory and antitumor activity but also significant toxicity. *A. niger* AS 3.739 transforms it to the less toxic metabolites 5α-hydroxytriptonide, triptolide (with a 14β-hydroxyl group), 17-hydroxytriptonide, and 16-hydroxytriptonide without hydrolyzing any of the three epoxide groups (Ning et al., 2003):

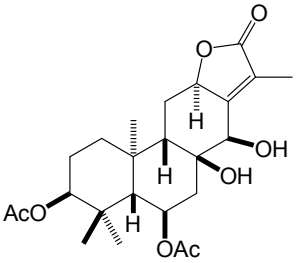


CCVII

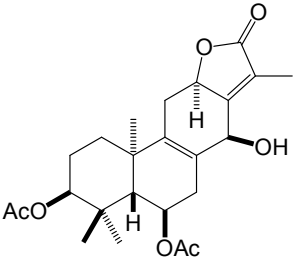
Gelomulide G (3β,6β-diacetoxy-8β,14β-epoxyabiet-13(15)-en-16,12-olide, **CCVIII**), a diterpenoid epoxy lactone from a tropical Asian plant with antileishmanial activity, when incubated with *A. niger* ATCC 10549 produces two metabolites, 3β,6β-diacetoxy-8β,14β-dihydroxyabiet-13(15)-en-16,12-olide (**CCIX**) and 3β,6β-diacetoxy-14β-hydroxyabiet-8(9),13(15)-dien-16,12-olide (**CCX**) (Choudhary et al., 2005):



CCVIII



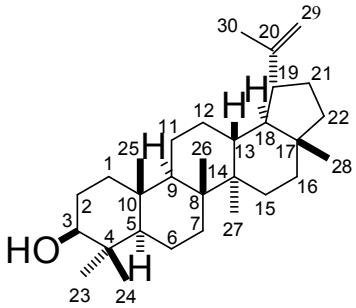
CCIX



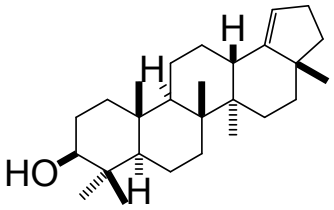
CCX

4. Transformation of triterpenoids

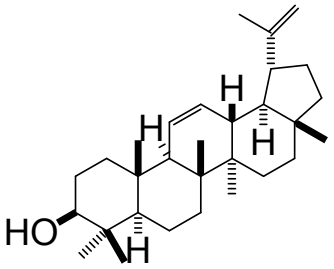
Several triterpenoids from plant essential oils are potential antimalarial drugs (Kaur et al., 2009). The lupanes are a group of pentacyclic triterpenoids that contain compounds with antimalarial activity (Suksamrarn et al., 2006; Kaur et al., 2009). *Aspergillus ochraceus* converted lupeol (**CCXI**) to two metabolites, **CCXII** (yield 19.0%) and **CCXIII** (yield 11.1%) in 10 days (Carvalho et al., 2010):



CCXI

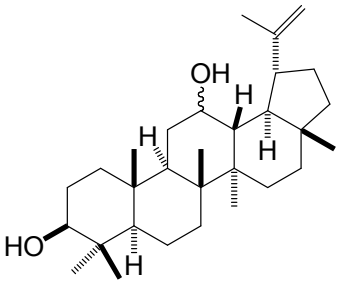


CCXII

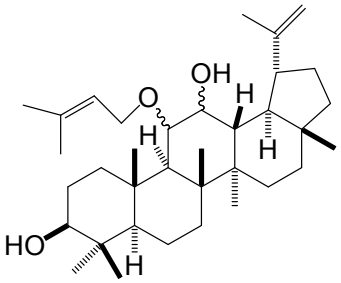


CCXIII

Also, *M. rouxii* transformed lupeol (**CCXI**) to two metabolites, **CCXIV** (yield 26.5%) and **CCXV** (yield 16.0%) in 10 days (Carvalho et al., 2010):

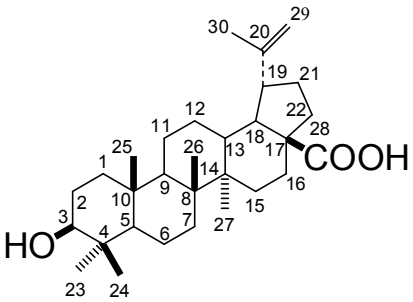


CCXIV

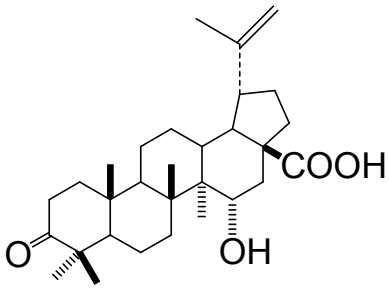


CCXV

The triterpenoids betulinic acid and betulonic acid are known to have antimalarial activity (Sá et al., 2009). Several fungi have been investigated for their ability to biotransform these compounds. For instance, *Colletotrichum* sp. transformed betulinic acid (**CCXVI**) to 3-oxo-15α-hydroxylup-20(29)-en-28-oic acid (**CCXVII**, yield 2.34%) (Bastos et al., 2007):

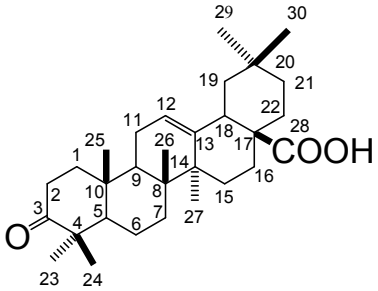


CCXVI

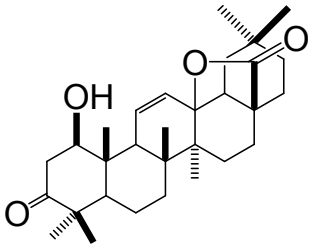


CCXVII

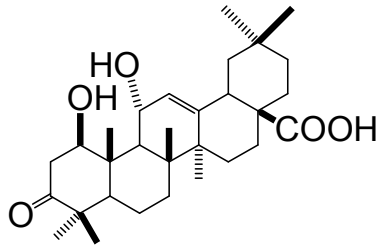
Some oleanolic acids from medicinal plants have been reported to be antimalarial (Cimanga et al., 2006; Kaur et al., 2009). The fungus *Absidia glauca* CGMCC 3.67 transformed 3-oxo-oleanolic acid (**CCXVIII**) to three new derivatives, 1β-hydroxy-3-oxo-olean-11-eno-28,13-lactone (**CCXIX**, yield 0.74%), 1β,11α-dihydroxy-3-oxo-olean-12-en-28-oic acid (**CCXX**, yield 2.3%) and 1β,11α,21β-trihydroxy-3-oxo-olean-12-en-28-oic acid (**CCXXI**, yield 0.23 %) (Guo et al., 2010):



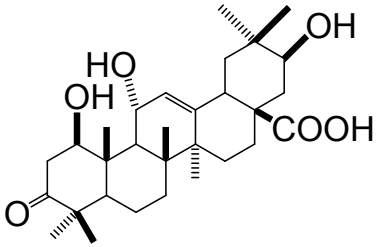
CCXVIII



CCXIX

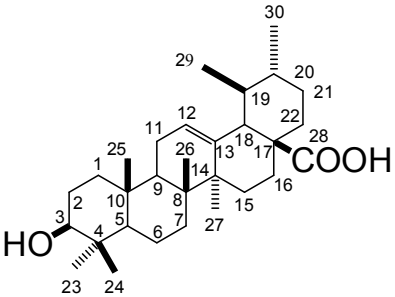


CCXX

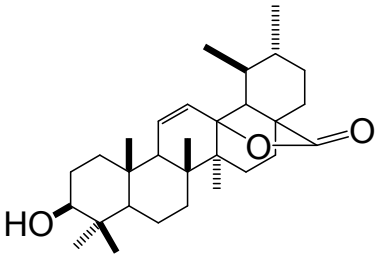


CCXXI

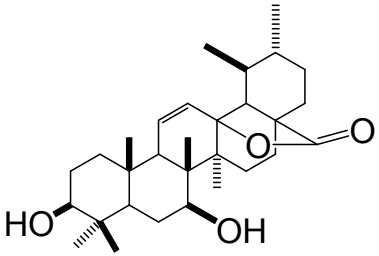
The triterpenoid ursolic acid, from the medicinal plant *Morinda lucida*, has been shown to have antimalarial activity (Cimanga et al., 2006). The soil fungus *Umbelopsis isabellina* converted ursolic acid (**CCXXII**) to three metabolites, 3β-hydroxy-urs-11-eno-28,13-lactone (**CCXXIII**, yield 0.69%), 3β,7β-dihydroxy-urs-11-eno-28,13-lactone (**CCXXIV**, yield 0.5%) and 1β,3β-dihydroxy-urs-11-eno-28,13-lactone (**CCXXV**, yield 0.88%) (Fu et al., 2011):



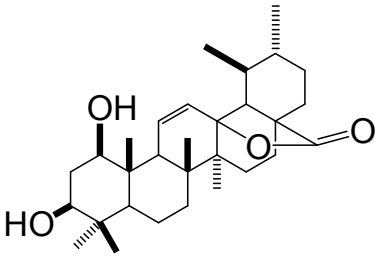
CCXXII



CCXXIII

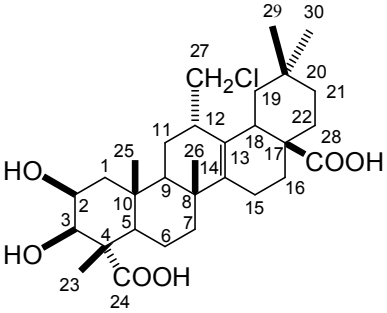


CCXXIV

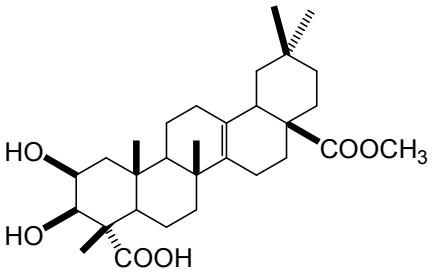


CCXXV

Transformation of another triterpenoid, senegenin (**CCXXVI**), by *Nocardia* sp. NRRL 5646 was accompanied by the formation of senegenic acid 28-methyl ester (**CCXXVII**) (Zhang et al., 2005):

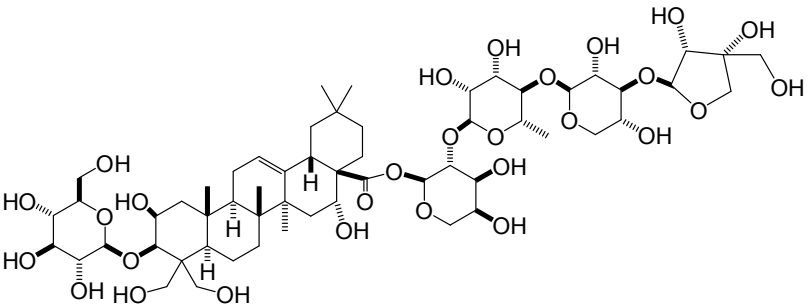


CCXXVI



CCXXVII

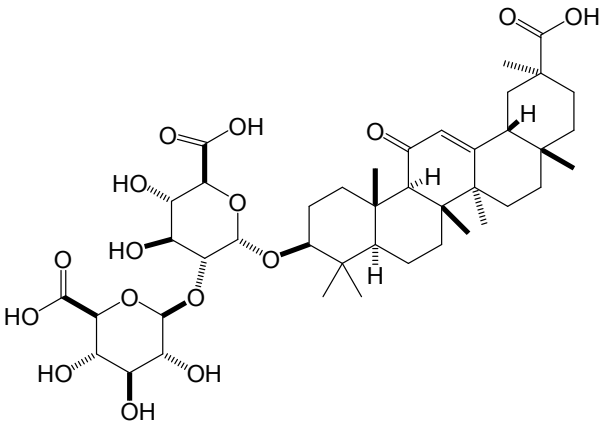
Platycodin D (**CCXXVIII**), a triterpenoid saponin with two side chains, from the root of the Asian bellflower, is transformed by a crude enzyme preparation from *A. niger* KCTC 6906 to a saponin lacking the terminal apiose and xylose of one side chain. This derivative has greater nitrite-scavenging activity and less toxicity (Wie et al., 2007):



CCXXVIII

A triterpenoid saponin derived from licorice, glycyrrhizic acid (glycyrrhizin, **CCXXIX**), is metabolized by a strain of *A. niger* that removes two glucuronic acid residues to produce the triterpenoids 7β,15α-dihydroxy-3,11-dioxo-oleana-12-en-30-oic

acid and 15α-hydroxy-3,11-dione-oleana-12-en-30-oic acid (Kang et al., 2008):

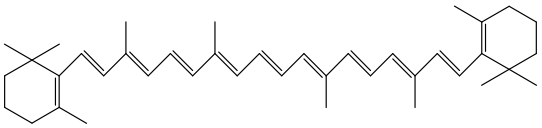


CCXXIX

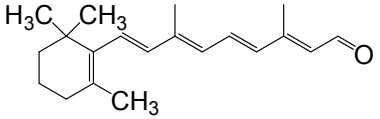
5. Transformation of tetraterpenoids

Carotenoids, an important group of tetraterpenoids found in nearly all plants, are often biotransformed for preparation of food additives and flavorings (Uenojo and Pastore, 2010). Biotransformation of β-carotene may produce retinoids, which can be used as raw materials for drugs and cosmetics (Jang et al., 2011), and some retinoids, including retinol, have antimalarial activity (Hamzah et al., 2003). A recombinant strain of *Escherichia coli* expressing β-carotene 15,15'-mono(di)oxygenase and the mevalonate pathway transformed β-carotene (**CCXXX**) to

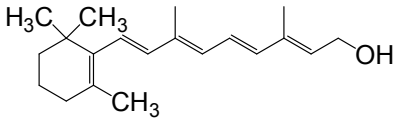
retinal (**CCXXXI**), the antimalarial retinol (**CCXXXII**) and retinyl acetate (**CCXXXIII**) (Jang et al., 2011):



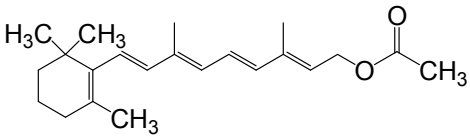
CCXXX



CCXXXI

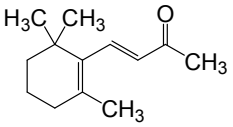


CCXXXII

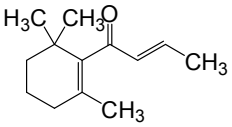


CCXXXIII

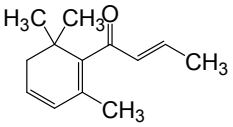
For the biotransformation of β-carotene, over 300 strains of microorganisms (bacteria, yeasts and filamentous fungi) were tested and seven unidentified strains showed transformation activity (Uenojo and Pastore, 2010). The isoprenoid chain of β-carotene (**CCXXX**) was cleaved with the formation of several products, including the principal product β-ionone (**CCXXXIV**), β-damascone (**CCXXXV**), β-damascenone (**CCXXXVI**), pseudoionone (**CCXXXVII**) and probably 1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene (**CCXXXVIII**) (Uenojo and Pastore, 2010):



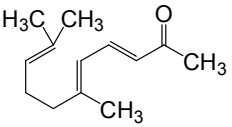
CCXXXIV



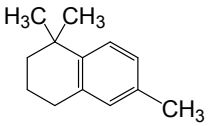
CCXXXV



CCXXXVI



CCXXXVII



CCXXXVIII

Conclusion

A work with terpenoids may suggest new biotransformation experiments that use fungi to produce new drug candidates. The most useful biotransformations should be amenable to improved methods and scale-up so that larger quantities of new metabolites may be made available for investigation.

Currently, artemisinin derivatives appear to be the most promising sources of new terpenoid antimalarial drugs. The main route selected by most researchers for the preparation of derivatives begins with chemical reduction of the carbonyl at position 10 of artemisinin to produce the toxic antimalarial compound dihydroartemisinin (Klayman, 1985; Li et al., 1998; Chaturvedi, 2011).

Arteether can be converted to several metabolites, not only by mammalian systems but also by fungi and bacteria (Vroman et al., 1999). Other chemical derivatives of artemisinin may be useful in the future for the microbial biosynthesis of new drugs with novel therapeutic properties. The combination of artemether with the unrelated drug lumefantrine is one of five artemisinin-based combinations currently recommended by the World Health Organization (WHO) for treatment of malaria (Omari et al., 2004; O'Brien et al., 2011). Various laboratories now are conducting research on hybrid trioxaquine molecules that have two different modes of action (Chauhan et al., 2010), such as a drug combining the structures of artemisinin and quinine that is highly effective against *P. falciparum* (Walsh et al., 2007).

The mechanisms of action of artemisinin and its derivatives on malaria parasites have not been completely studied, but there is evidence that the endoperoxide group plays an important role in antimalarial activity (Vroman et al., 1999; Muraleedharan and Avery, 2009; Fernández and Robert, 2011). The endoperoxide linkage breaks down under the influence of heme iron, with formation of an oxy free radical and then a carbon free radical, which interacts with proteins of the parasite to cause its death (Chaturvedi et al., 2010).

Some of the artemisinin derivatives, especially the trioxane dimers, are selectively cytotoxic; they have been shown not only

to target cancer cells by inducing apoptosis but also to prevent tumor growth by antiangiogenesis (Beekman et al., 1998; Posner et al., 2006; Nakase et al., 2008). The endoperoxide moiety required for antimalarial activity also appears to be required for cytotoxicity toward tumor cell lines (Beekman et al., 1998; Meunier and Robert, 2010). Therefore, in the development of microbial biotransformation processes for the derivatization of artemisinin, the endoperoxide group should be preserved.

Among the microbial biotransformation processes described here, the ones of greatest interest are those for the regiospecific and stereospecific hydroxylation of artemisinin and other antimalarial terpenoids because they increase solubility and provide sites for further modification (Medeiros et al., 2002; Parshikov et al., 2006). Microbial biotransformation procedures can be used to obtain terpenoid derivatives hydroxylated in almost any position, including some not obtainable by organic synthesis, such as 7β-hydroxyartemisinin (Parshikov et al., 2004b; Khor and Uzir, 2011). These metabolites may be used for further chemical or biological transformations that yield many potential candidate drugs from one compound.

Future research on antimalarial terpenoids should include studies of the biochemistry of the most useful biotransformations and of the antiplasmodial efficacy and toxicity of each of the metabolites. The compounds that are most effective against drug-

resistant strains of *P. falciparum* or *P. vivax* may be produced in higher yields by the use of biotechnology. New biotransformations of terpenoids, perhaps combined with chemical derivatization, may provide ways to overcome parasite resistance to currently used antimalarial drugs.

Hydroxylated derivatives of artemisinins obtained by microbial techniques may be used to create hybrid molecules based on molecules of nitrogenous heterocycles (Dovgilevich et al., 1991; Khasaeva et al., 2014; Modyanova et al., 1999, 2010; Parshikov et al., 1992, 1994, 1997, 1999a,b,c, 2000a,b,c,d, 2001a,b,c,d, 2002a,b,c,d, 2010b,c,d,e ; Sutherland et al., 2001; Terentyev et al., 1989, 1997, 2010; Williams et al., 2001, 2004; Williamson et al., 2007).

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